
4th International Kyoto Liver Cancer Symposium: Emerging Strategies to HCC

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Abstracts

Editor

Masatoshi Kudo, Osaka

Speaker's Curriculum Vitae

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Kinki University School of
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Masatoshi Kudo studied Medicine at Kyoto University and graduated in 1978. Following this, he completed a clinical fellowship in Kobe City General Hospital followed by a research fellowship at the University of California Davis Medical Center in USA and Kyoto University Graduate School of Medicine, where he received his PhD degree in Medical Science in 1987. Professor Kudo is currently a Professor and Chairman at the Department of Gastroenterology and Hepatology, Kinki University School of Medicine since 1999 and a President of Kinki University Medical Center since 2008.

Professor Kudo has published 476 International scientific peer review papers in well-regarded journals in addition to 786 domestic scientific papers. He has given 297 invited lectures in the area of his expertise on numerous occasions to international audiences. He serves as an Executive Council Board Member for Liver Cancer Study Group of Japan (LCSGJ), Chairman of Nationwide Survey Committee of LCSGJ, and a representative of LCSGJ Head Office. Professor Kudo is also an Executive Board Member of Japan Society of Hepatology (JSH), a Founding Board member of International Liver Cancer Association (ILCA). He is also serving as an Editor-in-Chief of *LIVER CANCER* (Karger).

His research interest is "Diagnosis and treatment of HCC". Professor Kudo is the first author of "Consensus-based Practice Manual of HCC Proposed by Japan Society of Hepatology" published in 2007 and 2010 revised version.

SS01-1

Emerging Role of CEUS

Masatoshi Kudo

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Objective: Almost all guidelines for the management of hepatocellular carcinoma (HCC) recommend B-mode ultrasonography (B-US) as the first-line screening tool in the surveillance of HCC worldwide. However, early detection of HCC using B-US is sometimes difficult because of coarse liver parenchyma associated with liver cirrhosis. Post-vascular phase images of contrast-enhanced ultrasonography (CE-US) with perfluorobutanemicrobubbles reportedly depict small HCC, even though B-US cannot depict any nodule in a cirrhotic liver. This prospective multicenter randomized controlled trial (RCT) was conducted to evaluate the efficacy of the post-vascular phase of CE-US in the surveillance of HCC.

Methods: From January 2009 to October 2012, 656 patients with liver cirrhosis associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) were enrolled and randomized into the B-US group and CE-US group. CE-US was performed 30–40 minutes after intravenous administration of Sonazoid®. HCC surveillance was performed in those patients every 3–4 months using B-US or CE-US. The primary endpoint was the size of HCC at the first detection.

Results: HCC was found in 95 of 622 eligible patients. The median follow-up period was 974 days. The annual incidence rate of HCC was 6.5%/year in total (5.5%/year in HBV patients, 7.1%/year in HCV patients). Tumor size at the first detection was 16.7 ± 6.2 mm by B-US and 13.0 ± 4.1 mm by CE-US ($p = 0.011$). In patients with HBV-related cirrhosis, tumor size was 14.5 ± 2.7 mm detected by B-US and 13.6 ± 6.0 mm by CE-US ($p = 0.715$). In patients with HCV-related cirrhosis, tumor size was 17.6 ± 7.0 mm detected by B-US and 12.7 ± 3.1 mm by CE-US ($p = 0.012$). The median period of initial detection was 297.5 days with B-US and 346.5 days with CE-US. Confirmation of HCC was possible in 65.4% of patients with B-US and 100% of patients with CE-US.

Conclusion: Our RCT results clearly show that post-vascular phase CE-US is superior to B-US in detecting small HCCs. Therefore, CE-US surveillance is strongly recommended for patients with cirrhosis, especially in patients with coarse liver parenchyma since cost of CE-US is much cheaper than dynamic CT or dynamic MRI.

Speaker's Curriculum Vitae

Name Kwang-Hyub Han
Institution Professor and Chairman of
Internal Medicine, Yonsei
University College of Medicine



Kwang-Hyub Han, MD is Professor and Chairman of Internal Medicine at Yonsei University College of Medicine, Seoul, Korea. He is also a Staff Gastroenterologist (Hepatologist) at Severance Hospital. He graduated Yonsei University College of Medicine in 1979. His research interests include the hepatitis virus and chronic liver diseases related to viral hepatitis B and C and hepatocellular carcinoma (HCC). His clinical research activities have included clinical trial and research on hepatitis B and C and HCC and he has been an invited speaker at a number of national and international scientific events. He is now current Director of Liver Cirrhosis Clinical Research Center, the president of the Korean Association for the Study of the Liver (KASL) and the first president of Asia-Pacific Primary Liver Cancer Expert (APPLE) Association. He is a member of a number of professional societies including the Korean Academy of Science Technology and AASLD. Professor Han has authored 286 publications in national and international peer-reviewed journals including The New England Journal of Medicine.

He is a reviewer for a number of journals including Hepatology, Journal of Hepatology and Journal of Gastroenterology and Hepatology and he has been served associate editor of Liver International. He was a member of the working party responsible for the Asian-Pacific consensus statement on the management of chronic hepatitis B.

SS01-2

The Role of Tumor Marker for Surveillance of HCC

Kwang-Hyub Han, Do Young Kim

Department of Internal Medicine, Yonsei University College of Medicine,
Seoul, Korea

The surveillance of hepatocellular carcinoma (HCC) is an established approach to detect early cancers in patients with high risks. Ultrasonography (US) and serum alpha-fetoprotein (AFP) remain the surveillance tests of choice and should be used in combination every 6 months until better surveillance tools become available. However, there are still controversial issues regarding the optimal surveillance methods. US has been the mainstay method for the surveillance of HCC. It has been reported that surveillance US has a sensitivity of between 65 and 80% and a specificity greater than 90%. At present, the sensitivity of AFP at the cutoff value of 20 ng/ml is around 60% and the specificity is ranging from 76 to 94%. Considering this limitation of serum AFP, the Western strategy of US without a biomarker such as AFP reflects the cost-effective utilization of limited resources. However, unlike Eastern countries, a significant portion of Western patients undergoing surveillance has obesity, which also makes it difficult to examine the entire liver thoroughly. In addition, US is highly dependent on the operator's experience. To improve the sensitivity of early diagnosis, additional test may be needed.

On the contrary, combined measurements of biomarkers in Eastern countries are based on the assumption that increased detection of early cancers could result in an overall survival benefit. Furthermore, serologic surveillance is intensively applied for the so-called 'super-high risk group' meaning cirrhotic patients in Japan using AFP, prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II), and AFP-L3. Importantly, this surveillance strategy is possible in Japan since it is fully reimbursed by the government.

Obviously, there is a difference in point of view regarding serologic surveillance for HCC between Western and Eastern hepatologists. For the Western perspective, the cost-benefit or efficiency is the primary concern because medical resources are limited. The increase in sensitivity achieved by combining tests is not cost-effective since there will be higher costs and false-positive results. Nonetheless, many physicians over the world use serum AFP measurement combined with US in order not to miss a small lesion on the cirrhotic background, which is barely detected even by experienced hands. It does not seem practical to remove AFP measurement from HCC surveillance in the absence of prospective study comparing US+AFP with US alone. It is helpful for us to remind that most of HCCs are in early stage in Japan where a shortened surveillance interval and combination of US and triple tumor markers such as serum AFP, AFP-L3 and PIVKA-II are already standard of care. Although the cost-effectiveness of surveillance is one of the most important factors to consider, the improvement of sensitivity to diagnose HCC at early stage is also one of important issues.

Speaker's Curriculum Vitae

Name Morris Sherman, MB, BCh, PhD,
FRCP(C)
Institution University of Toronto



Dr. Morris Sherman graduated in medicine from the University of the Witwatersrand in Johannesburg South Africa in 1972. He completed his internship and residence at the Baragwanath Hospital in Johannesburg and Groote Schuur Hospital in Cape Town. He completed his PhD at the University of Cape Town in 1982 and he moved to New York to do post-doctoral training at the Albert Einstein College of Medicine in New York. In 1984 he was appointed to the Toronto General Hospital and went on staff at the University of Toronto.

Dr. Sherman has over the previous years been president of the Canadian Association for Study of the Liver, chairman of the Canadian Viral Hepatitis Network and is currently President of the Canadian Liver Foundation. Together with Dr. Jordi Bruix he authored the North American guidelines for the management of HCC in 2005, and again in 2011. He has served as chairman of the AASLD special interest group on HCC. He was also a founding member, and is now treasurer of the International Liver Cancer Association.

Dr. Sherman's interests have been in the management of viral hepatitis and screening and management of HCC.

SS01-3

Tumor Marker is NOT Necessary

Morris Sherman

University of Toronto, Canada

Although screening for hepatocellular carcinoma (HCC) is common practice there continues to be debate about the most appropriate method of screening. Most of the debate is about the use of biomarkers. No-one disputes the use of ultrasound. To understand the place of biomarkers it is first necessary to determine what we want screening to achieve, and at what cost. Screening must reduce the likelihood of dying of HCC. To do this screening must identify HCC at a stage when there is a high likelihood of cure. This means finding HCC that is smaller than about 2.0 to 2.5 cm in diameter. The likelihood of curing these tumours is about 80%. As the tumour gets larger at diagnosis the likelihood of cure decreases. The question then is not whether adding biomarkers to ultrasound improves the tumour detection rate, but whether addition of biomarkers to ultrasound improves the cure rate. Put another way, does it matter whether the tumour is found at 1.0 cm or 2.0 cm in diameter. The data would suggest that it does not matter.

The second question is whether biomarkers do provide earlier detection, and the evidence on this is scanty. All three of the commonly used biomarkers AFP, AF-L3 and DCP are markers of advanced or aggressive disease. A screening test meant to find early disease cannot also be a marker of advanced or aggressive disease. This is because these screening tests are unlikely to result in improved cure rates.

Finally, the question must be asked whether the use of biomarkers results in more false-positive screening tests, leading to unnecessary investigations. AFP in particular is associated with a high false-positive rate that diminishes its possible usefulness.

In conclusion, the data supporting that the use of biomarkers improves survival is weak. Cost efficacy data suggest that addition of AFP increases costs without benefit.

Speaker's Curriculum Vitae

Name Ryosuke Tateishi
Institution Department of Gastroenterology,
Graduate School of Medicine,
The University of Tokyo



Dr. Ryosuke Tateishi has been working on hepatocellular carcinoma (HCC) since 1998 when he started his PhD in Hepatology at the University of Tokyo, Japan where he graduated in 2002. During his PhD, he studied the prognostic factors of patients with HCC and developed a new scoring system named Tokyo Score. Since 2013, he has been Project Associate Professor at the Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo where he continues working on diagnosis and treatment of HCC, particularly on those who underwent percutaneous treatment. He is currently a member of Committee for the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Liver Cancer Study Group of Japan and Working Committee for Japanese Clinical Practice Guideline for Liver Cancer. Dr. Tateishi published >100 international scientific papers in high quality English Journal including Gastroenterology, Hepatology, Gut and Journal of Hepatology.

SS01-4

Surveillance Interval Should Be Shorter for Cirrhotic Patients

Ryosuke Tateishi, Kazuhiko Koike

Department of Gastroenterology, Graduate School of Medicine,
The University of Tokyo, Japan

Hepatocellular carcinoma (HCC) is the fourth most common cause of death in Japan with 34,000 deaths occurring annually. Approximately 65% and 15% of HCC patients in Japan is due to chronic hepatitis C and B, respectively. As the number of ultrasonographic (US) examinations practicable in an institution is limited, it is reasonable to change the interval of US according to the risk of HCC in order to average the number of patients diagnosed as HCC per one US examination. Annual incidence of HCC among cirrhotic patients due to hepatitis B and hepatitis C is extremely high in Japan, reported to be 7–8%. The annual incidence is as high as 3–5% even in pre-cirrhotic patients. Thus, it is widely accepted in Japan to shorten the interval of ultrasonography in cirrhotic patients to 3–4 month as the efficiency of the surveillance is comparable to that with 6 month interval in European countries. Although US plays a major role in the surveillance for HCC, its accuracy is significantly affected by the various factors including operator's skill, performance of the equipment, liver parenchymal atrophy and coarseness and patient's obesity. Since it is more difficult to detect small HCC nodules in cirrhotics than in non-cirrhotic liver, tumor size at diagnosis tends to be larger in patients with advanced cirrhosis. Since the majority of those patients is not suitable for resection, shorter interval of examination may increase the number of patients with small HCC suitable for percutaneous ablation or liver transplantation. Actually in our cohort of 313 patients who were diagnosed as HCC during surveillance, partly contributed by three tumor markers, only 10% of them showed tumors larger than 3 cm in diameter.

Speaker's Curriculum Vitae

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Masatoshi Kudo studied Medicine at Kyoto University and graduated in 1978. Following this, he completed a clinical fellowship in Kobe City General Hospital followed by a research fellowship at the University of California Davis Medical Center in USA and Kyoto University Graduate School of Medicine, where he received his PhD degree in Medical Science in 1987. Professor Kudo is currently a Professor and Chairman at the Department of Gastroenterology and Hepatology, Kinki University School of Medicine since 1999 and a President of Kinki University Medical Center since 2008.

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SS01-5

GIDEON Final Analysis Data: Regional Difference

Masatoshi Kudo

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Osaka-Sayama, Japan

Introduction: GIDEON is a global, prospective, non-interventional study evaluating patients with unresectable hepatocellular carcinoma (uHCC) treated with sorafenib in clinical practice. Completion of GIDEON created a large database of >3000 sorafenib-treated patients across 39 countries and 5 regions, allowing for assessment of regional differences in treatment history, practices, and outcomes.

Methods: Baseline disease characteristics were collected on patients for whom a decision to treat with sorafenib had been made in clinical practice. Dosing and outcomes data were collected during follow-up.

Results: 3202 patients comprised the safety population. While patients in Japan tended to be diagnosed at an earlier disease stage, the majority had progressed to Barcelona Clinic Liver Cancer (BCLC) stage C by the start of sorafenib therapy. Time from initial diagnosis to the start of sorafenib treatment was 6–20 times longer in Japan than in other regions (Table). A greater proportion of patients in Japan received prior locoregional treatment (84%) or surgery (43%) compared with the US (locoregional treatment, 49%; surgery, 9%) or EU (locoregional treatment, 44%; surgery 16%). In Japan, more patients discontinued sorafenib due to disease progression (37%) and adverse events (27%) compared with other regions (range: 3–26% and 3–17%, respectively). Fewer patients were lost to follow-up in Japan (<1%) than in other regions (range: 6–25%). In the intent-to-treat (ITT) population (n = 3213), median overall survival (OS) from the start of sorafenib therapy was longest in Japan, whereas median time to progression (TTP) was shortest. Patients in Japan also had the longest median time from initial diagnosis to death, irrespective of BCLC stage (Table).

Conclusion: This final analysis of GIDEON confirms regional variations in treatment practices and outcomes in uHCC patients. In particular, patients in Japan tend to be diagnosed earlier and receive a greater number of treatments compared with other regions.

	Overall (n = 3202)	AP (n = 928)	EU (n = 1113)	LA (n = 90)	US (n = 563)	Japan (n = 508)
BCLC stage A/B/C/D at initial diagnosis ^a (% of n)	22/20/30/3	9/16/38/3	24/26/32/2	23/31/23/8	17/12/27/6	44/20/18/1
BCLC stage A/B/C/D at start of sorafenib therapy ^a (% of n)	7/20/52/5	3/10/61/5	9/24/53/4	18/40/29/9	10/12/36/12	7/32/55/2
Median OS from start of sorafenib therapy ^b (months)	10.9	9.7	11.8	13.7	8.5	14.5
Median TTP from start of sorafenib therapy ^b (months)	4.8	3.8	6.4	15.2	5.5	3.4
Median time from initial diagnosis to start of sorafenib therapy (months)	3.9	2.6	3.7	1.2	2.8	24.1
Median time from initial diagnosis to death ^b (months): overall	25.5	20.9	25.0	19.5	14.8	79.6
BCLC A (n = 686)	59.2	54.0	49.3	23.3	24.9	91.0
BCLC B (n = 633)	29.9	31.0	27.3	22.2	19.7	47.9
BCLC C (n = 973)	10.6	10.3	11.0	11.2	8.5	27.7
BCLC D (n = 91)	8.9	8.9	11.0	NA	7.5	13.1

^a Missing/not evaluable patients not tabulated; ^b Based on ITT population (n = 3213; AP = 955, EU = 1115, LA = 90, US = 553, Japan = 500).
AP = Asia-Pacific; LA = Latin America; NA = not available

Speaker's Curriculum Vitae

Name Michiie Sakamoto
Institution Department of Pathology, Keio University School of Medicine



Education:

1985 MD, Keio University School of Medicine
1989 D.Med.Sci., Keio University Graduate School of Medicine

Brief Chronology of Academic Appointments:

1989– Research member, Pathology Division, National Cancer Center Research Institute
1996– Head of Section, Pathology Division, National Cancer Center Research Institute
1996–1997 Visiting Research Fellow, The Burnham Institute (Dr. Erkki Ruoslahti)
1999– Chief, Pathology Division, National Cancer Center Research Institute
2002– Professor, Department of Pathology, Keio University School of Medicine
2009– Vice-dean, Keio University School of Medicine

Societies:

The Japanese Society of Pathology (Executive Director)
The Japanese Cancer Association (Councilor)
The Japan Society of Hepatology (Councilor)
American Association for Cancer Research
Liver Cancer Study Group of Japan (Permanent Secretary)

Honors and other Recognition:

Tamiya Memorial Award, 2000
The Japanese Society of Pathology; Pathology Research Award 2001

Editors:

Editor-in-chief: Pathology International
Associate Editor: Cancer Science, Hepatology Research, Keio Journal of Medicine
Editorial Board: Japanese Journal of Clinical Oncology, etc

Speciality and Research Field of Interest:

Molecular Pathology of Cancer (Liver, Pancreas, etc) and Pathology Informatics

SS02-1

Pathology of Early HCC

Michiie Sakamoto, Hidenori Ojima, Yohei Masugi

Department of Pathology, Keio University School of Medicine, Japan

Through careful and detailed follow-up of high-risk cases, early hepatocellular changes have been classified from dysplastic foci, dysplastic nodules (low-grade and high-grade), and early through to advanced HCC. Early HCC is defined as vaguely nodular well differentiated HCC, and the diagnosis of cancer is made based on histological atypia and presence of stromal invasion. However, definite distinction between DN and early HCC may be difficult by morphology alone. Recently several immunohistochemical markers have been developed to assist the diagnosis in this regard. Positive expression of HSP70, GPC3, GS and some other markers support the diagnosis of cancer. Though there still remain sensitivity and specificity requires careful evaluation, combination of these markers can raise the diagnostic accuracy. It should also be noted that some early HCC show similar molecular-profiles as advanced HCC, suggesting gradual transition to more malignant lesions. In contrast, no positive markers have been identified to be useful for diagnosis of DNs. Conceptually, pathologic diagnosis represents malignant potential of the lesions. However, gray zone exist between LRN and LGDN; LGDN and HGDN; and HGDN and early HCC. Therefore, we are considering to propose grading of early HCC, which will help to establish practically useful pathologic diagnosis of early hepatocellular lesions.

Speaker's Curriculum Vitae

Name Osamu Matsui
Institution Department of Advanced Medical
Imaging, Kanazawa University
Graduate School of Medical
Sciences



Dr. Osamu Matsui is a graduate of Kanazawa University Faculty of Medicine in 1972 and completed radiology residency at Kanazawa University hospital. He was promoted to full professor and chairman for the Department of Radiology, Kanazawa University in 1999. In 2010, he was appointed for the dean of Kanazawa University Graduate School of Medical Science, and is now the specially appointed research professor of the Department of Advanced Medical Imaging and professor of emeritus at the same institute. His main clinical and research contributions have been in the diagnostic imaging and interventional radiology, especially for liver cancer. He is now an associate editor of gastrointestinal section of Radiology. He was selected one of the distinguished scientists of Japan in 2009 by the Minister of Education, Culture, Sports, Science and Technology.

SS02-2

Molecular Backgrounds of Gd-EOB-DTPA Enhanced MRI in Pathological Early HCC*Osamu Matsui¹, Azusa Kitao², Taro Yamashita³, Yasuni Nakanuma⁴, Shuich Kaneko³*

¹Department of Advanced Medical Imaging, Kanazawa University Graduate School of Medical Sciences, Japan; ²Department of Radiology, Kanazawa University Graduate School of Medical Sciences, Japan; ³Department of Gastroenterology, Kanazawa University Graduate School of Medical Sciences, Japan; ⁴Department of Pathology, Kanazawa University Graduate School of Medical Sciences, Japan

In human hepatocytes, there are various membrane transporters. Among them, Gd-EOB-DTPA is suspected to be uptaken by OATP families including OATP1B1, OATP1B2, OATP1B3, and OATP1B4, and excreted by MRP2 into bile ducts. The majority of hypervascular HCCs show definite hypointensity on HB phase of EOB-MRI but around 6–15% hyperintensity. The quantitative analysis of the expression of mRNA of transporters revealed that the grade of OATP1B3 (synonym with OATP8) expression was significantly higher in hyperintense HCCs than in hypointense HCCs. However, no significant difference was observed in other OATPs and MRP2. Immunohistochemical staining of OATP1B3 revealed definite expression in hyperintense HCCs but not or less in hypointense HCCs. There is a significant correlation between the grade of OATP1B3 expression and tumor enhancement ratio on HB phase of EOB-MRI. Therefore, HB phase of EOB-MRI is an extremely sensitive (indirect) molecular imaging for hepatocyte uptake transporter OATP1B3 expression in HCC cells. Semiquantitative analysis of immunohistochemistry of OATP1B3 revealed that its expression was significantly decreased in accordance with the elevation of the grade of malignancy of the nodules from dysplastic nodule to poorly differentiated HCCs. In addition, OATP1B3 expression already decreased in around 85% of pathological early HCC. Our recent genetic analysis revealed a significant positive correlation between HNF4 α and OATP1B3 expression in HCC cells. The decrease of HNF4 α or its function in hepatocytes was reported to be one of the important initiators of inflammation-related human hepatocarcinogenesis. Taken all together, OATP1B3 expression can be decreased in the early stage of hepatocarcinogenesis, and its decrease is considered to be a sensitive biomarker of early stage hepatocarcinogenesis, resulting in very high sensitivity of EOB-MRI in the detection of “pathological early HCC”.

Speaker's Curriculum Vitae

Name Tomoaki Ichikawa
Institution Department of Radiology,
University of Yamanashi



1988–1989	Internship, Chiba University Hospital
1992–1998	Staff, Department of Radiology, University of Yamanashi
1998–1999	Research Fellow, Department of Radiology, University of Pittsburgh Medical Center
1999–2004	Assistant Professor, Department of Radiology, University of Yamanashi
2004–2006	Visiting Associate Professor, Department of Radiology, Brigham & Women's Hospital, Harvard Medical School
2006–Present	Associate Professor, Department of Radiology, University of Yamanashi

SS02-3**Diagnosis of Pathological Early HCC with EOB-MRI:
Japanese Experience***Tomoaki Ichikawa*

Department of Radiology, University of Yamanashi, Japan

Recently, the International Consensus Group for Hepatocellular Neoplasia (ICGHN) arrived at a conclusion regarding the pathological criteria for early hepatocellular carcinoma (e-HCC) after much debate. They especially stated that stromal invasion should be recognized as the most important pathological finding for e-HCC differentiating from dysplastic nodule (DN).

We conducted to review imaging findings of multi-imaging modalities of e-HCCs confirmed according to the pathological criteria of the ICGHN compared with those of DNs. The multi-imaging modalities included contrast-enhanced multidetector-row CT (CE-CT), unenhanced MRI, EOB-enhanced MRI (EOB-MRI), CT during arteriography (CTAP), and CT during hepatic arteriography (CTHA).

Diagnostic performances of all imaging modalities except for EOB-MRI for evaluating e-HCC were proven to be unsatisfactory. Finally, significantly high detectability for e-HCC was only observed with hepatocyte-phase EOB-MRI (30/31, 97%). The significant imaging features to distinguish between e-HCCs and DNs were hypointensity of e-HCC on hepatocyte-phase EOB-MRI: All of e-HCC which was detected on hepatocyte-phase EOB-MRI (30/30, 100%) showed hypointensity, while all of DNs showed iso or hyperintensity compared to liver parenchyma. The results of the diagnostic performance showed that EOB-MRI had outstanding sensitivity (97%) for detecting e-HCC and specificity (100%) for differentiating e-HCC from DN. Thus, EOB-MRI is the only imaging modality that shows perfect ability in the detection and classification of e-HCC based on the imaging findings of "hypointensity on hepatocyte-phase EOB-MRI". Meanwhile, hepatologists/radiologists should recognize that there is a given number of e-HCC that may show iso or hyperintensity on hepatocyte-phase EOB-MRI, resulting in impossible differentiation from DNs.

Recent reports and our results have indicated that signal intensity patterns of e-HCC on hepatocyte-phase EOB-MRI correlate closely and maybe directly with the degree of expression of organic anion transporting polypeptide (OATP)1B3 in the nodules. Thus, the excellent diagnostic performance with EOB-MRI may be introduced in pathological diagnosis by using OATP1B3 staining method.

Speaker's Curriculum Vitae

Name Jeong Min Lee, MD, PhD
Institution Professor,
Department of Radiology,
College of Medicine Seoul National
University Hospital



Jeong Min Lee studied Medicine at Chonbuk National University and graduated in 1986. Following this, he completed a clinical fellowship in Chonbuk National University Hospital and Chungnam National University, where he received his PhD degree in Medical Science in 2004. Professor Lee is currently a Professor at the Department Radiology, College of Medicine Seoul National University Hospital since 2012 and Chief Radiologist of Abdominal Imaging and nonvascular intervention section.

Professor Lee has published 234 International scientific peer review papers in well-regarded journals in addition to 45 domestic scientific papers. He has given 154 invited lectures in the area of his expertise on numerous occasions to international audiences. He serves as a chairman of scientific committee of Korean Society of Radiology. He is also serving as Reviewer for *Radiology*, *AJR*, *European Radiology*, and *Journal of magnetic Resonance Imaging*.

His research interest is "Imaging Diagnosis of abdominal diseases, new body MR imaging techniques, and minimally invasive treatment of HCC".

SS02-4

Differentiation of Early HCC from DN: Korean Experience

Jeong Min Lee

Department of Radiology, College of Medicine Seoul National University Hospital, Korea

The development of hepatocellular carcinoma (HCC) in cirrhotic liver is described either as de novo hepatocarcinogenesis or as a multistep progression, from low-grade dysplastic nodule to high-grade dysplastic nodule, then to dysplastic nodule with microscopic foci of HCC, then to small HCC, and finally to overt carcinoma. Therefore, early detection and accurate assessment of small HCC is of great importance as the therapeutic efficacy of various treatments and the survival of patients with small HCC are much more successful than those for patients with larger tumors. The detection of small hepatocellular nodules and precise characterization, however, remain the most challenging area in imaging the cirrhotic liver. A variety of imaging modalities, including ultrasound (US), computed tomography (CT), magnetic resonance (MR), nuclear medicine, and angiography, have been used in evaluating patients with chronic liver disease and suspected HCC. Experiences in numerous institutions have established that contrast-enhanced MR imaging and CT scan are highly specific in diagnosing hepatic tumors, but are not sensitive enough to detect early changes of HCC such as early HCC. Recent technologic advances in MR imaging including tissue specific contrast agents such as hepatocyte-specific agent (Gd-EOB-DTPA), will undoubtedly have a major impact on liver nodule imaging. Gd-EOB-DTPA facilitate the imaging of both the vascular and hepatobiliary phase in the liver, and is able to provide information regarding hemodynamic features and hepatocyte functions of focal liver lesions. As hepatobiliary phase imaging can provide functional information of the hepatocytes and the focal liver lesions, it is very useful for detecting borderline cirrhotic nodules. Several previous studies have shown that this contrast agent has led to further improvement in the detection rates of focal hepatic lesions. In this lecture, I will review the current Gd-EOB-DTPA-enhanced MR imaging techniques, and its role for evaluation of hepatocarcinogenesis and cirrhosis-related borderline lesions.

Speaker's Curriculum Vitae

Name Rita Golfieri, MD
Institution Head of the Radiology Unit and Vice Director of Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna



Dr. Rita Golfieri obtained her Medical Degree in 1979, Specialization in Radiology in 1983 and in Neurology in 1989 at the University of Bologna, Italy. During 1980–2000 she was Registrar and then Consultant of Diagnostic and Interventional Radiology at Sant'Orsola-Malpighi University Hospital of Bologna, where in 1990 she became Head of the Vascular and Interventional Unit. In 1989, she spent a year as a Visiting Assistant of Radiology at Mount Vernon Hospital and Royal Marsden Hospital in London, UK. During 2000–2003 she was nominated Head of the Department of Radiology at the Hospital of Forlì, Italy. From 2003 to now she held the same position in Bologna, being also Vice Director of the Department and Professor in the Postgraduate School of Radiology and Gastroenterology and Degree Course for Radiographers at the University of Bologna. In 2014 she obtained the National Scientific Qualification for the position of Full Professor in the Discipline of Diagnostic Imaging, Radiotherapy and Neuroradiology.

Member of RSNA (Radiologic Society of North America), ESR (European Society of Radiology), SIRM (Società Italiana di Radiologia Medica), CIRSE (Cardiovascular and Interventional Radiology), ESGAR (European Society of Gastrointestinal and Abdominal Radiology) and speaker at more than 300 Meetings and Conferences, she has authored or co-authored more than 500 scientific articles (120 in peer-reviewed journals), 12 books and 42 chapters of books. H index: 20 (Scopus); Total Impact factor: 436.

She is a Reviewer of *European Radiology*, *Radiographics*, *Journal of Hepatology*, *Investigative Radiology*, *La Radiologia Medica*, *Liver Transplantation and Digestive and Liver Diseases*.

Her main scientific interests include abdominal and liver diagnostic and interventional radiology.

SS02-5**EOB-MRI: European Experience***Rita Golfieri*

Head of the Radiology Unit and Vice Director of Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, Italy

The newly introduced magnetic resonance imaging (MRI) contrast agent, gadoxetic acid (Gd-EOB-DTPA), has enabled concurrent assessment of tumor vascularity and unique hepatocyte-specific contrast during the hepatobiliary (HB) phase which can help in detecting and characterizing smaller HCCs and in its early phase, appearing hypointense during the hepatocyte phase. In small lesions (≤ 2 cm) the HB-phase is 11% more sensitive in the classification of HGDN/early HCC than dynamic MRI, with an added value of 32.5% in the NPV. On the HB-phase of EOB-MRI images, typical HCC, early HCCs and high-grade dysplastic nodules appear as a hypointense nodular lesion whereas a low-grade dysplastic or a regenerative nodule appears as an iso- or hyperintense lesion. The HCC hypointensity during the HB phase is explained by decreased expression of OATP with high expression of MRP2. In fact, the HB phase of gadoxetic acid-enhanced MR imaging led to the frequent identification of atypical HCC nodules difficult to be detected by ultrasonography or computed tomography, not showing the diagnostic patterns of arterial wash-in and portal/delayed washout. These nodules can either display a hypervascular pattern in the arterial phase, without portal washout and hypointense appearance in the HB-phase of EOB-MRI or they can be hypovascular both on the arterial and portal phases with hypointensity on the hepatocyte phase (hypovascular hypointense nodules). It is already well recognized that these newly diagnosed entities can be high-grade dysplastic nodules or early HCCs (vaguely nodular type), which are difficult to differentiate, even at needle biopsy.

In the size range of ≤ 2 cm nodules in cirrhotic liver under US surveillance, the incidence of these atypical nodules is high (33%) and they are frequently malignant (32%). Among HCC nodules sizing 1–2 cm, the prevalence of atypical hypovascular pattern varies around 11–18%. The diagnostic accuracy of EOB-MRI for the diagnosis of early HCC is around 95–100%. Hypovascular HCC and high-grade dysplastic nodules can grow and acquire a more extensive arterial supply, and show overt stromal invasion (invasive growth of tumor tissue in portal tracts and fibrous septa), during stepwise carcinogenesis of HCC. In patients with chronic liver disease, one third of the hypovascular nodules showing hypointensity in the HB-phase became hypervascular, with a 1 and 3-year cumulative incidence of 25% and 41%. Hypovascular nodules containing fat, hyperintense on T2W and DWI images or those that were greater than 10–15 mm in diameter or showing a growth rate with a doubling time >542 days were at higher risk for development of hypervascularization, thus becoming typical HCC. Therefore, these hypovascular nodules should be strictly followed up or definitely treated as a typical HCC.

In contrast, some HCCs are hyperintense during HB-phase because of high OATP expression with decreased MRP2 expression or high OATP expression with high expression of MRP2 in luminal membranes of pseudoglands. Hyperintense HCCs on HB phase images showed significantly higher differentiation grades, less frequent portal vein invasion, and lower recurrence rates than did hypointense HCCs. Hyperintense HCCs on HB-phase may be a particular form of HCC with biologically less aggressive features than those of hypointense HCCs.

Due to these intrinsic capabilities of identifying precursors and biological behavior of HCC, EOB-MRI has rapidly become a key-imaging tool for the diagnosis of HCC and its precursors despite the problems associated with scarce MRI availability through Europe. It has been demonstrated that performing EOB-MRI before deciding on curative treatment for early-stage HCC may improve the accuracy of treatment decision for early-stage HCC.

Speaker's Curriculum Vitae

Name Tatsuo Inoue
Institution Department of Gastroenterology
and Hepatology, Kinki University



1999–2000 Trainee doctor , Kinki University Hospital
2000–2002 Trainee doctor, Kitano Hospital
2002–2005 Graduate student, Department of Gastroenterology, Kinki
University School of Medicine
2005–2009 Research Associate, Department of Gastroenterology, Kinki
University School of Medicine
2009–Present Lecturer, Department of Gastroenterology, Kinki University
School of Medicine

SS02-6**Natural Course and Role of Contrast-Enhanced
Ultrasonography***Tatsuo Inoue, Masatoshi Kudo*

Department of Gastroenterology and Hepatology, Kinki University, Japan

Recent progress in imaging modality, especially Gd-EOB-DTPA MRI, is starting to play a very important role in the imaging diagnosis of hepatic tumors. Hypointense lesions in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI that show non hypervascularity on dynamic imaging are commonly encountered, and it is recommended that these lesions be monitored closely due to their potential for malignancy and transitioning to HCC through a multistep progression of hepatocarcinogenesis. The 2010 revisions of the diagnostic algorithms for hypovascular HCC, as presented in the consensus-based clinical practice manual edited by the Japan Society of Hepatology in 2007, also recommends to evaluate a kupffer phase image of Sonazoid-enhanced ultrasonography (US) when we encounter such non hyperascular lesions. Nationwide study in Japan has found that kupffer phase image of sonazoid-enhanced US [Exp(B): 3.684, 95% CI = 1.798–7.546, $p = 0.0004$] and tumor diameter [Exp(B): 1.086, 95% CI = 1.027–1.148, $p = 0.004$] can be a useful factor to predict hyper vascularization of borderline lesions detected as hypo intence on hepatobiliary phase of Gd-EOB-DTPA MRI.

Speaker's Curriculum Vitae

Name Fabio Piscaglia, MD, PhD
Institution Division of Internal Medicine, Alma Mater Studiorum, University of Bologna



Graduated in October 1992 at the School of Medicine in Bologna. Prize for the best curriculum of the students graduated in 1991/92.

1993 member of the Italian Association for the Study of the Liver (AISF) and of the Italian Society for Ultrasound in Medicine and Biology (SIUMB). Start of research activities in the fields of liver disease and ultrasound. Awarded a one year research grant for an investigation on Doppler Ultrasound in portal hypertension

1997 Complete pass of the *United States Medical License Examination (USMLE)*.

1997–1998 *one year period at the University of Goettingen, Germany*, devoted to basic research in liver fibrogenesis.

1998 *Specialization in Internal Medicine* at the University of Bologna, Department of Internal Medicine and Gastroenterology

1998–2002 *PhD program in Ultrasound in Human and Veterinary Medicine*

2000 General Secretary of the WFUMB (World Federation of Societies for Ultrasound in Medicine and Biology) congress, held in Florence. >2500 attendees

2001–2004 Research fellow at the University of Bologna, Division of Internal Medicine, Dept of Internal Medicine and Gastroenterology

2005–current Assistant Professor at the University of Bologna, Division of Internal Medicine. Chairman of the Center for Ultrasound in Internal Medicine, where more than 8000 US are carried out yearly, including more than 80 interventional procedures and >700 contrast enhanced ultrasound exams per year. Consultant for the Liver Transplant Program and coordinator of the hospital bimonthly Liver Oncology meetings. Responsible for the Liver Cancer Outpatient Service in the Unit of Internal Medicine, chairman prof. L. Bolondi
2008–2011 Member of the Governing Board of the Italian Association for the Study of Liver Disease.

2011–2013 President of the European Federation of Societies for Ultrasound in Medicine and Biology (28 Nations, over 20.000 members)

2011–present Member of the Board of Directors of the International Contrast Ultrasound Society (ICUS)

2009 Director of the Euroson School on Contrast Enhanced Ultrasound in Liver, Biliary, Pancreatic and Gastrointestinal Disease, Bologna Sept 16–18

2013 Promoter and member of the steering committee and senior author of the EFSUMB Guidelines and Recommendations on the clinical use of ultrasound Elastography. Part 1, Technology (Ultraschall Med, in press April 2013) and Part 2, Clinical (Ultraschall Med, in press June 2013)

2013 Winner of European Marie Curies funding project in conjunction with a Spanish Academic Center and a Spanish Small Enterprise (total 1.300.000 approx) for the period 2013–2017 on the use of Contrast Enhanced Ultrasound in prognostication of patients with portal hypertension

Articles in PubMed 168. (53 as first author). Total Impact Factor >600 (ISI 2009)

Scientific interest: *Liver Cancer, Liver Transplantation, Liver fibrosis, Portal Hypertension*

Peer reviewer for several (>15) international scientific journal with an Impact Factor >1

Invited speaker at 6 EASL congresses or single topic conferences from 2005

SS03-1

CEUS Should Be Included in the Guideline

Fabio Piscaglia, Giulia Allegretti

Division of Internal Medicine, Alma Mater Studiorum, University of Bologna, Italy

CEUS is able to depict the typical vascular pattern of enhancement of hepatocellular carcinoma (HCC), corresponding to homogeneous hyperenhancement in the arterial phase followed up by wash-out in the venous phase. However this pattern is observed also in approximately 50% of the cases of mass forming peripheral CholangioCellular Carcinoma (CCC) arising in cirrhosis. At variance, the latter entity (CCC) usually (but not always) doesn't show wash-out at contrast enhanced CT or MRI, due to the different pharmacokinetics of CT/MRI and ultrasound contrast agents. For these reasons and specifically the risk of false positive diagnosis of HCC in case of CCC, CEUS, initially introduced in the American (AASLD) guidelines in 2005, was dropped from both the 2011 AASLD and the 2012 EASL guidelines for the diagnosis of HCC. However, the same choice was not made by other continental and national important hepatology societies (Asian, Japanese, Italian). The pattern of hyperenhancement+wash out at CEUS may not imply a 100% Positive Predictive Value for HCC, but it is anyhow nearly totally specific for malignancy. Conversely CCC may show hyperenhancement in the arterial phase at CT/MRI, but tend to lack venous wash-out, as it happens in some non malignant (especially in some high grade dysplastic) hepatocellular nodules. This means that no definitive diagnosis is possible by CT/MRI imaging alone by the latter techniques (not even of benign versus malignant nature) in case of CCC. The lack of a diagnostic pattern for CCC at CR/MRI would imply a biopsy, whose false negative rate at first attempt is reported as high as 35% in small nodules (Forner, Hepatology 2008). Moreover, the rate of CCC among newly developed liver nodules has been repeatedly reported to range between 0.5 and 2%. Thus, since only half CCC show the typical HCC pattern, the risk of misdiagnosis would be less than 1% of newly developed nodules. Furthermore, in most instances, a misdiagnosis would not affect the treatment strategy (e.g. surgical resection), thus making the impact of misdiagnosis of smaller impact. Moreover, some subtle CEUS features, such as rapid and marked wash-out tend to suggest the possibility of CCC, based on expert opinion and some scatter reports, making this concept endorsed by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB). Briefly, it has to be acknowledged that the "typical" CEUS pattern of HCC may include a $\leq 1\%$ risk of CCC and that the role of such risk of misdiagnosis has been differently weighted by various hepatology societies. On practical grounds, CEUS is usually less sensitive than CT or MRI in detecting wash-out, whereas it is highly sensitive in identifying arterial hyperenhancement thanks to its real time modality. Hence, in the instance in which CEUS shows a typical malignant pattern, but discrepant from CT or MRI (which are always recommended to stage the disease), with wash-out detected only by CEUS but not by CT/MRI, a high suspicion of CCC should arise. When instead wash-out is not detected by CEUS, but it is present at CT/MRI a diagnosis of HCC is reached, with the lack of wash out at CEUS suggesting a more differentiated tumor than in cases where wash-out is present at all imaging modality.

Based on these reasons, CEUS should not be excluded from the imaging techniques able to provide a diagnosis of HCC, once the above reported cautions are taken into consideration, according to the Italian and the Japanese Societies for the Study of the Liver. CT or MRI remain to be held as primary and most cost-effective techniques, given also the fact that they are needed to stage the disease before any treatment is provided. However, this should not exclude CEUS, since in a not negligible rate of cases biopsy cannot be carried out due to technical reasons (clotting impairment, unsafe needle track path, ascites...) and CT and or MRI could be suboptimal (poor patient cooperation) or contraindicated (claustrophobia, renal failure, etc). Moreover CEUS is safe, cheap and easily repeatable and can well complement some limitations of "heavy" radiologic techniques.

Speaker's Curriculum Vitae

Name Namiki Izumi, MD, PhD
Institution Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital



Education

1978, March Graduated from Department of Medicine, Tokyo Medical and Dental University

Professional Experience

1978–1980 Resident in medicine, in associated hospital of Tokyo Medical and Dental University
1980–1986 Fellow in the second department of Internal Medicine, Tokyo Medical and Dental University
1986–1990 Associated Director of Medicine, Musashino Red-Cross Hospital
1991–2008 Director, Chief of Gastroenterology and Hepatology, Musashino Red-Cross Hospital
2005– Invited Professor of Gastroenterology and Hepatology, Kinki University
2006– Clinical Professor, Tokyo Medical and Dental University
2008– Vice President of Musashino Red-Cross Hospital

Academic Membership

2008–2011 Chief Investigator of study group of data mining analysis for chronic hepatitis C in Japanese Ministry of Health, Welfare and Labor
2012– Chief Investigator of study group of clinical study in viral hepatitis and hepatocellular carcinoma including Japan Red Cross Hospital Association, supported by Japanese Ministry of Health, Welfare and Labor
2009– Board Member of Japanese Society of Hepatology
2010– Board Member of Japanese Association for Liver Cancer

Guideline committee member of viral hepatitis of Japan Society of Hepatology
Guideline committee member of hepatocellular carcinoma in Japan Society of Hepatology
In 2014, President of 50th anniversary meeting of Japan Society of Hepatology in Tokyo
In 2016, President of 52nd meeting of Japan Liver Cancer Study Group

SS03-2

Japanese Algorithm for Diagnosis of Early Stage of HCC*Namiki Izumi, Kaoru Tsuchiya, Yutaka Yasui, Masayuki Kurosaki*

Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Japan

Background: Nowadays, more than 60% of HCC nodules are detected in early stage of smaller than 2 cm in diameter, because extensive surveillance has been carried out by ultrasound or contrast-enhanced CT scan in the patients infected with hepatitis B or C virus. Therefore, the diagnostic algorithm for the diagnosis of HCC is important issue in Japan. For the purpose of establishing diagnostic algorithm of early stage of HCC, Japanese study group for the establishing early stage of HCC supported by Japanese Ministry of Health, Welfare and Labor presented a new algorithm including Gd-EOB DTPA enhanced MRI and contrast-enhanced ultrasound, in addition with contrast-enhanced CT scan.

Methods: 150 patients with hypovascular nodules in the liver defined by contrast-enhanced CT and/or MRI in whom pathological findings were confirmed by needle biopsy or surgical resection were analyzed from 8 established Japanese high volume center.

Results: Among the 150 hypovascular nodules, 147 nodules showed hypointensity at hepatocyte phase in Gd-EOB DTPA enhanced MRI. When the 147 hypointense nodules were divided by the diameter of the nodule of 1.5 cm, 14.5% of them were moderately or poorly differentiated HCC, and 66.5% were well-differentiated HCC, and the frequency of moderately or poorly differentiated HCC was not different between the nodules smaller than 1.5 cm. When the hypointense nodules at hepatocyte phase by Gd-EOB DTPA enhanced MRI were divided by the diameter of the nodule of 1.0 cm, 12.5% of the nodules were moderately or poorly differentiated HCC, and 70.5% of the nodules were well differentiated HCC, histologically, and the frequency of moderately or poorly differentiated HCC was not different between the nodule smaller than 1.0 cm. Half of moderately or poorly differentiated HCC revealed hypoechoic lesion in Kupffer phase under contrast-enhanced ultrasound using Sonazoid. From these results, moderately or poorly differentiated HCC has characteristic imaging findings of hypointensity in hepatocyte phase by hepatocyte phase of Gd-EOB DTPA enhanced MRI and hypoechoic lesion in Kupffer phase by contrast-enhanced ultrasound.

Conclusion: New diagnostic algorithm was established in early stage of HCC using Gd-EOB DTPA enhanced MRI and contrast-enhanced ultrasound. The hypoechoic nodules in Kupffer phase by contrast-enhanced ultrasound in the hypointense nodules in hepatocyte phase by Gd-EOB DTPA enhanced MRI should be treated extensively, even the nodule diameter was smaller than 1.5 cm.

Speaker's Curriculum Vitae

Name Byung Ihn Choi, MD, PhD
Institution Seoul National University Hospital



Born in Korea, Dr. Choi received his medical degree in 1974 from the College of Medicine at Seoul National University. After stints as a visiting radiologist and visiting professor at universities from Tokyo through San Francisco, Houston and New York to Boston, he was appointed to a professorship at his alma mater in 1994.

Many of Dr. Choi's opportunities to foster global alliances in medical imaging application and research have come from participation and leadership in numerous subspecialty societies.

Dr. Choi previously served as presidents of the Korean Society of Ultrasound in Medicine, the Korean Society of Radiology, Asian Federation of Societies for Ultrasound in Medicine and Biology, Asian Oceanian Society of Radiology, and Asian Society of Abdominal Radiology.

And also was presidents of the organizing committee of the 11th Congress of the World Federation for Ultrasound in Medicine and Biology, and the 12th Asian Oceanian Congress of Radiology.

Dr. Choi is a prolific researcher and educator. Dr. Choi's main research interest is in hepatobiliary and gastrointestinal imaging with ultrasound, CT and MRI. He has given more than 600 invited lectures including 345 international lectures. He has published over 400 peer-review scientific articles, 28 book chapters and 1 monograph and has received numerous grants from government, industry and private sources.

He has won over 70 different awards from many different professional organizations. Among the dozens of international awards he has received are honorary fellowship from American College of Radiology, the European Society of Gastrointestinal and Abdominal Radiology and the American Institute of Ultrasound in Medicine, and honorary membership from Radiological Society of North America, European Society of Radiology, German Society of Radiology and Australasian Society of Ultrasound in Medicine, and gold medallist of Asian Federation of Societies of Ultrasound in Medicine and Biology.

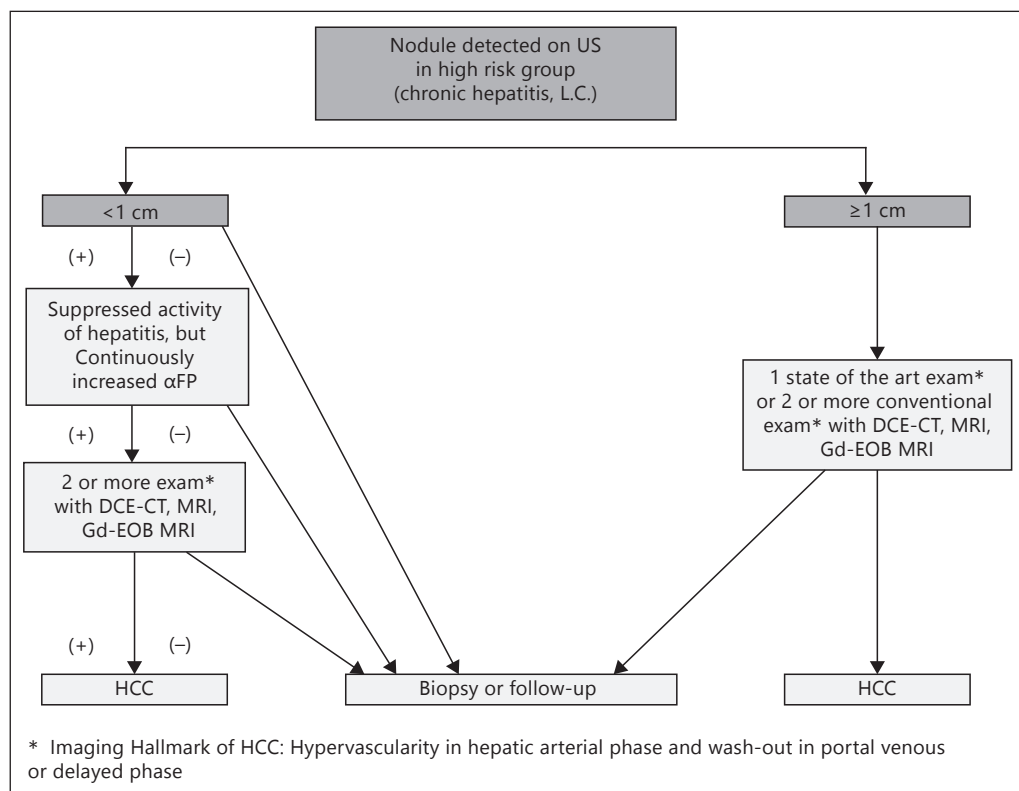
SS03-3

Diagnostic Algorithm of HCC in Korea

Byung Ihn Choi

Seoul National University Hospital, Korea

Revised version 2014 (Tentative)



Speaker's Curriculum Vitae

Name Osamu Matsui
Institution Department of Advanced Medical
Imaging, Kanazawa University
Graduate School of Medical
Sciences



Dr. Osamu Matsui is a graduate of Kanazawa University Faculty of Medicine in 1972 and completed radiology residency at Kanazawa University hospital. He was promoted to full professor and chairman for the Department of Radiology, Kanazawa University in 1999. In 2010, he was appointed for the dean of Kanazawa University Graduate School of Medical Science, and is now the specially appointed research professor of the Department of Advanced Medical Imaging and professor of emeritus at the same institute. His main clinical and research contributions have been in the diagnostic imaging and interventional radiology, especially for liver cancer. He is now an associate editor of gastrointestinal section of Radiology. He was selected one of the distinguished scientists of Japan in 2009 by the Minister of Education, Culture, Sports, Science and Technology.

SS03-4

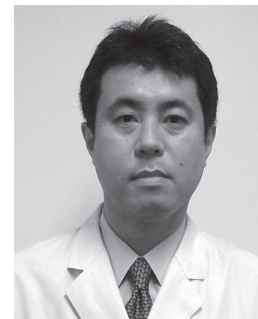
Proposal of New Diagnostic Algorithm Based on Gd-EOB-DTPA Enhanced MRI*Osamu Matsui¹, Sigeki Arii², Masatoshi Kudo³*

¹Department of Advanced Medical Imaging, Kanazawa University Graduate School of Medical Sciences, Japan; ²President, Hamamatsu Rousai Hospital, Japan; ³Department of Gastroenterology, Kinki University Faculty of Medicine, Japan

After the introduction of Gd-EOB-DTPA enhanced MRI (EOB-MRI) in Japan, the imaging diagnosis of HCC has been drastically changing in clinical practice. Therefore, there is an increasing need to develop a simple HCC diagnostic algorithm centered on EOB-MRI. Accordingly, a new HCC diagnostic algorithm was proposed in March 2012 by the research group (headed by Dr. Shigeki Arii) funded by the Ministry of Health. This algorithm basically recommends the implementation of EOB-MRI in cases where HCC is suspected by B-mode ultrasound findings and tumor marker measurements. The diagnosis of HCC is made when a nodule shows hypervascularity in the arterial phase and washout in the portal dominant phase. HCC is also diagnosed when a nodule is hypervascular in the arterial phase and hypointense in the hepatobiliary phase, even if washout in the portal phase is not obvious (with the exclusion of hemangioma by other sequences of MRI). When a hypervascular nodule is hyperintense in the hepatobiliary phase, HCC can be diagnosed when the capsule or mosaic structure is apparent. Biopsy is recommended if the diagnosis is not definitive. On the other hand, if a nodule is hypovascular in the arterial phase and hypointense in the hepatobiliary phase, contrast-enhanced ultrasonography (US) using Sonazoid is required to confirm hypervascularity or defects in the Kupffer phase in order to make a definitive diagnosis of HCC. If hypervascularity or defects in the Kupffer phase are absent, lesions more than 1 cm in diameter should be biopsied and those less than 1 cm need to be followed up. Furthermore, institutions unable to conduct MRI as initial diagnostic imaging need to perform dynamic CT first, followed by EOB-MRI as the recommended diagnostic method. CTAP/CTHA, SPIO-MRI and should be performed as an optional at each institution. This proposal was accepted by the many experts at the Symposium of the 48th Annual Meeting of the Liver Cancer Study Group of Japan held in July, 2012.

Speaker's Curriculum Vitae

Name Taro Yamashita, MD, PhD
Institution Department of Gastroenterology,
Kanazawa University Hospital



Taro Yamashita is an Assistant Professor at the Kanazawa University Hospital, Japan. He is a graduate of the Kanazawa University and completed his gastroenterology residency at the Kanazawa University Hospital. He spent three years as a visiting fellow at the Laboratory of Human Carcinogenesis, NCI-Bethesda. He returned to Japan as an Assistant Professor of Department of Gastroenterology in 2008.

His research interests include the classification of liver cancer based on molecular profiling approaches and the development of novel treatment strategies targeting liver cancer stem cells.

Representative Publication:

1. Yamashita T, Kitao A, Matsui O, Hayashi T, Nio K, Kondo M, Ohno N, Miyati T, Okada H, Yamashita T, Mizukoshi E, Honda M, Nakanuma Y, Takamura H, Ohta T, Nakamoto Y, Yamamoto M, Takayama T, Arii S, Wang XW, Kaneko S. Gd-EOB-DTPA-enhanced Magnetic Resonance Imaging and Alpha-fetoprotein Predict Prognosis of Early-Stage Hepatocellular Carcinoma. *Hepatology* 2014 In Press.
2. Yamashita T, Wang XW. Cancer stem cells in the development of liver cancer. *J Clin Invest* 2013 (123) 1911–1918.
3. Yamashita T, Honda M, Nakamoto Y, et al: Discrete Nature Of EpCAM+ and CD90+ Cancer Stem Cells in Human Liver Cancer. *Hepatology* 2013 (57) 1484–1497.
4. Yamashita T, Honda M, Nio K, Nakamoto Y, Takamura H, Tani T, Zen Y, Kaneko S. Oncostatin M Renders Epithelial Cell Adhesion Molecule-Positive Liver Cancer Stem Cells Sensitive to 5-Fluorouracil by Inducing Hepatocytic Differentiation. *Cancer Res* 2010 (70) 4687–4697.
5. Yamashita T, Ji J, Budhu A, Forgues M, Yang W, Wang HY, Jia H, Ye Q, Qin LX, Wauthier E, Reid LM, Minato H, Honda M, Kaneko S, Tang ZY, Wang XW. EpCAM-Positive Hepatocellular Carcinoma Cells Are Tumor-Initiating Cells With Stem/Progenitor Cell Features. *Gastroenterology* 2009 (136) 1012–1024.
6. Yamashita T, Forgues M, Wang W, Kim JW, Ye Q, Jia H, Budhu A, Takafuji V, Zanetti KA, Chen Y, Qin LX, Tang ZY, Wang XW. A combined expression of EpCAM and a-fetoprotein defines a novel prognostic subtype of hepatocellular carcinoma. *Cancer Res* 2008 (68) 1451–1461.
7. Yamashita T, Budhu A, Forgues M, Wang XW. Activation of hepatic stem cell marker EpCAM by Wnt- β -catenin signaling in hepatocellular carcinoma. *Cancer Res* 2007 67(22) 10831–10839.

Honors:

1. American Association for the Study of Liver Diseases (AASLD), Young Investigator Travel Award, 2004
2. Gastroenterology Research Group/American Gastroenterological Association (GRG/AGA), Young Investigator Award, 2005
3. The Japan Society of Hepatology (JSH), OTSUKA Award, 2010
4. Viral Hepatitis Research Foundation of Japan, Distinguished Research Award, 2011
5. The Japanese Society of Gastroenterology (JSGE), Research Grant Award, 2011
6. Japan Institute of Invention and Innovation (JIII), Invention Prize, 2013
7. Kanazawa Medical Institute Memorial Award, 2013

Editorial:

1. Editorial Board, PLoS ONE
2. Associate Editorial Board, American Journal of Cancer Research
3. Editorial Board, Journal of Cancer Research and Therapeutic Oncology
4. Review Editor, Frontiers in Cell and Developmental Biology
5. Editorial Board, World Journal of Hepatology

SS04-2

Diversity of Cancer Stem Cells in Hepatocellular Carcinoma

Taro Yamashita, Masao Honda, Shuichi Kaneko

Department of Gastroenterology, Kanazawa University Hospital, Japan

Carcinogenesis could be characterized as deregulated malignant organogenesis mediated by abnormally proliferating and/or metastatic cancer cells and activated stromal cells that trigger angiogenesis, fibrosis, and inflammation at site. Liver cancer development may recapitulate fetal liver development in part in terms of emergence of cells expressing certain stem cell markers and the activation of signaling pathways during the liver development. Cancer cells and stem cells have similar capacity in view of self-renewal, limitless division, and generation of heterogeneous cell population. The cancer stem cell (CSC) concept, a subset of cells bearing stem cell features that is indispensable for tumor development and perpetuation, has recently been accepted by accumulating evidences. Although CSCs have been identified using several stem cell markers and are now considered a pivotal target for the eradication of hepatocellular carcinoma, little information is known about the characteristics of each-marker-positive cells. Here we provide several evidences that liver CSCs defined by EpCAM and CD90 show unique features of tumorigenicity/metastasis with phenotypes closely associated with committed liver lineages, indicating that liver CSCs are not a single, static entity. The presence of CD90⁺ cells was associated with high incidence of distant organ metastasis within two years after surgical resection, and CD90⁺ CSCs showed the molecular features of vascular endothelial cells with abundant expression of c-Kit and chemosensitivity to imatinib mesylate. These data suggest that clinical outcomes of liver cancer may correlate with the presence of certain CSCs with distinct biological features.

Speaker's Curriculum Vitae

Name Osamu Nakashima, MD, PhD
Institution Department of Clinical Laboratory
Medicine, Kurume University
Hospital



Work Experience:

Department of Clinical Laboratory Medicine, Kurume University Hospital

Education and Qualifications:

- 1983; Graduated from Kurume University School of Medicine
- 1983–1985; First Department of Internal Medicine, Kurume University School of Medicine
- 1985–2004; Department of Pathology, Kurume University School of Medicine (1994; instructor, 2004; associate professor)
- 2004–2006; Chief, Department of Laboratory Medicine, National Hospital Organization Kyushu Medical Center
- 2006–2011; Associate professor, Department of Pathology, Kurume University School of Medicine
- 2011–present; Professor, Department of Clinical Laboratory Medicine, Kurume University Hospital

Belonging Medical Society:

- Japanese Society of Laboratory Medicine
- The Japanese Society of Pathology
- The Japanese Society of Clinical Cytology
- The Japan Society of Hepatology
- Liver Cancer Study Group of Japan
- The Japan Society of Ultrasonics in Medicine
- International Liver Cancer Association

SS04-3

Tumor Marker and Hepatocellular Carcinoma (HCC)

Osamu Nakashima¹, Hisamitsu Miyaaki², Shuji Sumie³, Koji Okuda⁴,
Michio Sata³, Hirohisa Yano⁵

¹Department of Clinical Laboratory Medicine, Kurume University Hospital, Japan; ²First Department of Internal Medicine, Nagasaki University School of Medicine, Japan; ³Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Japan; ⁴Division of Hepato-Biliary-Pancreatic Surgery, Kurume University School of Medicine, Japan; ⁵Department of Pathology, Kurume University School of Medicine, Japan

α -Fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA) II are well known as tumor markers of hepatocellular carcinoma (HCC), and their diagnostic usefulness has been confirmed. It has been reported that an increase of lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and PIVKA II in HCC patients tends to be related to a poor prognosis.

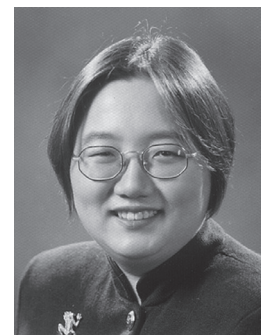
Regarding relation of gross classification and tumor marker, the single nodular type with extra nodular growth or the confluent multinodular type was significantly higher than the single nodular type in AFP-L3-positive cases, PIVKA II-positive cases, and cases positive for both. Portal vein invasion was found more frequently in the patients positive for either marker than in those negative for either, and more frequently in patients positive for both AFP-L3 and PIVKA II than in those negative for both. PIVKA II was useful predisposing parameter for the development of portal vein invasion and intrahepatic metastasis, because intrahepatic metastasis of HCC occurs via the portal vein. AFP-L3 positivity was high in poorly differentiated HCCs in comparison with PIVKA II positivity, whereas PIVKA II positivity was high in HCCs with portal vein invasion or intrahepatic metastasis in our data.

Microvascular invasion (MVI) has been recognized as a risk factor for outcome following curative resection in HCC. MVI classification (as no, mild and severe) can stratify HCC patients by different patterns of recurrence and risk of survival after curative resection. Patients with severe MVI had significantly higher elevated AFP and PIVKA II levels compared with patients without MVI or with mild MVI. Patients with severe MVI had larger tumors and significantly higher prevalence of HCC that was poorly differentiated and had intrahepatic metastasis.

Many HCCs with a diameter less than 2 cm were negative for both AFP-L3 and PIVKA II, showing that for detection of early-stage HCCs, AFP-L3 and PIVKA II should be used in combination with other appropriate tumor markers or imaging modalities.

Speaker's Curriculum Vitae

Name Young Nyun Park, MD, PhD
Institution Vice Dean for Graduate Affairs and
Avison Distinguished Professor,
Department of Pathology,
Yonsei University College of
Medicine



Professor Young Nyun Park studied medicine at Yonsei University and graduated in 1987, and she earned PhD from Yonsei University College of Medicine in Seoul, Korea, in 1994. Following this, she studied liver pathology at Mount Sinai Medical Center in the US. She started her academic career in 1996 as assistant professor and became a professor in the Department of Pathology at Yonsei University College of Medicine, in 2006. She has been appointed to the Vice Dean for Graduate Affairs of Yonsei University College of Medicine since 2008.

Professor Park has published about 160 peer reviewed papers in international journals, including Hepatology, Journal of Hepatology, American Journal of Pathology, etc. She has contributed to the sections of hepatocellular carcinoma and combined hepatocellular-cholangiocarcinoma in the 4th edition of WHO Classification of Tumours of the Digestive System in 2010 and the textbook entitled Practical Hepatic Pathology published by Elsevier in 2011. She has received 15 awards, including the best research awards from the Korean Society of Pathologists in 2006, the Korean Association for the Study of the Liver in 2002, Seoul Medical Association in 2013, and Yonsei University in 2010, 2011, and 2013.

Professor Park's academic memberships include the Asian Pacific Association for the Study of the Liver, the American Association for the Study of Liver Diseases, the US and Canadian Academy of Pathology, the Korean Society of Pathologists, the Korean Association for the Study of the Liver, the Korean Academy of Science and Technology, the Hans Popper Hepatopathology Society, APPLE, Laennec Society on Liver Pathology, etc. She is serving as an academic editor of PLoS ONE, an editorial board member for Hepatology.

Her research has focused on understanding the early stage of hepatocarcinogenesis and cancer stem cells of hepatocellular carcinoma.

SS04-4

Scirrhou Pattern and EMT in HCC

Young Nyun Park

Department of Pathology and BK21 PLUS Project for Medical Science,
Yonsei University College of Medicine, Seoul, Korea

Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) are the major primary liver cancers in adults. The phenotypic overlap between HCC and CC has been shown to comprise a continuous liver cancer spectrum. As a proof of this concept, a recent study demonstrated a genomic subtype of HCC that expressed CC-like gene expression traits, such as CC-like HCC, which revealed the common genomic trait of stem-cell-like properties and aggressive clinical outcomes. Scirrhou HCC, a rare variant of HCC, is characterized by abundant fibrous stroma and has been known to express several liver stem/progenitor cell markers. This suggests that scirrhou HCC may harbor common intermediate traits between HCC and CC, including stem-cell traits, which are similar to those of CC-like HCC. However, the molecular and pathological characteristics of scirrhou HCC have not been fully evaluated. By performing gene-expression profiling and immunohistochemical evaluation, we compared the morphological and molecular features of scirrhou HCC with those of CC and HCC. Scirrhou HCC expresses both stem-cell-like and CC-like genomic traits. In addition, we observed the expression of core epithelial-mesenchymal transition (EMT)-related genes, which may contribute to the aggressive behavior of scirrhou HCC. Overexpression of transforming growth factor beta (TGF- β) signaling was also found, implying its regulatory role in the pathobiology of scirrhou HCC. Conclusion: We suggest that the fibrous stromal component in HCC may contribute to the acquisition of stem-cell-like and/or CC-like gene-expression traits in HCC. The expression of TGF- β /EMT molecules may play a pivotal role in the aggressive phenotyping of scirrhou HCC.

Speaker's Curriculum Vitae

Name Michiie Sakamoto
Institution Department of Pathology, Keio University School of Medicine



Education:

1985 MD, Keio University School of Medicine
1989 D.Med.Sci., Keio University Graduate School of Medicine

Brief Chronology of Academic Appointments:

1989– Research member, Pathology Division, National Cancer Center Research Institute
1996– Head of Section, Pathology Division, National Cancer Center Research Institute
1996–1997 Visiting Research Fellow, The Burnham Institute (Dr. Erkki Ruoslahti)
1999– Chief, Pathology Division, National Cancer Center Research Institute
2002– Professor, Department of Pathology, Keio University School of Medicine
2009– Vice-dean, Keio University School of Medicine

Societies:

The Japanese Society of Pathology (Executive Director)
The Japanese Cancer Association (Councilor)
The Japan Society of Hepatology (Councilor)
American Association for Cancer Research
Liver Cancer Study Group of Japan (Permanent Secretary)

Honors and other Recognition:

Tamiya Memorial Award, 2000
The Japanese Society of Pathology; Pathology Research Award 2001

Editors:

Editor-in-chief: Pathology International
Associate Editor: Cancer Science, Hepatology Research, Keio Journal of Medicine
Editorial Board: Japanese Journal of Clinical Oncology, etc

Speciality and Research Field of Interest:

Molecular Pathology of Cancer (Liver, Pancreas, etc) and Pathology Informatics

SS04-5

Wnt/ β -Catenin Activated Typical Subclass of HCC

Michiie Sakamoto, Kathryn Effendi, Ken Yamazaki, Mariko Fukuma

Department of Pathology, Keio University School of Medicine, Japan

Typical pathologic findings of HCC are cohesive tumor nests associated with rich vascular stroma. Series of genetic studies indicated that the most frequently mutated oncogene or tumor suppressor gene in HCC is β -catenin. Molecular subclassification based on gene expression signature proposed a typical hepatocyte-like subclass of HCC harboring this gene mutation which showed a more differentiated histology with a less aggressive clinical outcome. We previously identified that LGR5 is frequently overexpressed in HCC with β -catenin mutation. LGR5 is known as one of the downstream target genes of Wnt signaling pathway, however its functional role in cancer has been largely unknown. We demonstrated that cells transfected with LGR5 established higher colony forming activity, and were more resistant to a cytotoxic drug than cells transfected with empty vector. Overexpression of LGR5 inhibited cell motility. LGR5-transfected cells formed nodule type tumors in the livers of immunodeficient mice, whereas empty vector-transfected cells formed more invasive tumors. These suggest that aberrant expression of LGR5 regulates epithelial cell phenotype and survival of HCC and moreover, represent a typical phenotype of HCC.

Speaker's Curriculum Vitae

Name Yonson Ku
Institution Department of Surgery, Division of
Hepato-Biliary-Pancreatic Surgery,
Kobe University Graduate School of
Medicine



Professor Ku studied Medicine at Kobe University School of Medicine and graduated in 1977. After the graduation, he completed his clinical fellowship at Kobe University Hospital followed by a research fellowship at University of Tennessee in USA and receipt of PhD degree in Medical Science in 1983. Professor Ku is currently a professor at Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine since 2005.

Professor Ku has published 208 international scientific papers in well-characterized journals in addition to 272 domestic scientific papers in Japan. He serves as executive directors of many Japanese Academic societies (Japanese Society of Gastroenterological Surgery, Japanese Society of Gastroenterology, Japan Society of Clinical Oncology) and councilors such as Japan Society for Transplantation, Japan Society of Hepatology, Japanese society of Hepato-Biliary-Pancreatic Surgery.

His research interests and life work are to build a novel strategy for treatment of advanced hepatocellular carcinoma combined with or without Percutaneous Isolated Hepatic Perfusion (PIHP), which was invented with his leadership from his group. His achievement is well characterized from his successive research fundings from Japanese Ministry of Educational Grants, and also from his recent book chapters in Surgery of the Liver, Biliary Tract and Pancreas: "Isolated Hepatic Perfusion for Extensive Liver Cancers" published in 2007 and Induction Chemotherapy: "Induction Chemotherapy for Hepatocellular Carcinoma" published in 2011 and Radiologic and Surgical Practice: "Venous Embolization of the Liver" published in 2011.

SS05-2

Reductive Hepatectomy with Percutaneous Isolated Hepatic Perfusion as the First-Line Treatment for Hepatocellular Carcinoma with Multiple Bilobar Lesions*Yonson Ku, Takumi Fukumoto*Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery,
Kobe University Graduate School of Medicine, Japan

Background and Aim: There are several studies regarding reductive hepatectomy for advanced multiple hepatocellular carcinoma (HCC). The usual strategy of reductive hepatectomy is to resect large, life-threatening lesions that are difficult to treat with loco-regional therapies, and transcatheter arterial chemoembolization (TACE) or transcatheter arterial infusion is then given to treat residual tumors in the remnant liver. However, there was considerable heterogeneity between studies in terms of inclusion criteria, the extent of tumor involvement and type of additional treatment for residual tumors. The efficacy and benefit of reductive hepatectomy for advanced multiple HCC remains unclear. The aim of this study was to report a 20-year single center experience of reductive hepatectomy for patients with far advanced HCC with multiple bilobar lesions combined percutaneous isolated hepatic perfusion (PIHP).

Methods: Until December 2012, 95 patients with advanced bilobar HCC were performed reductive hepatectomy. These patients were not candidates for surgical resection with curative intent or local ablative therapies because of the location, number ($n > 5$), size or bilobar distribution of their liver tumors. TACE was also not indicated because of major portal tumor thrombi or diffuse bilobar liver tumors that required non-selective whole-liver TACE. Patient received planned PIHP with mitomycin C 20–40 mg/m² and/or doxorubicin 60–120 mg/m² 1–3 months after reductive hepatectomy.

Results: In 95 patients with distinctive main tumors, 74 had major hepatectomies: left lobectomies ($n = 11$); extended left lobectomies ($n = 9$); right lobectomies ($n = 44$); extended right lobectomies ($n = 9$); and anterior and medial segmentectomy ($n = 1$). Thrombectomies were simultaneously performed in 32 patients with Vp4 PVTT. Ten patients were unable to receive PIHP because of liver function deterioration after reductive hepatectomy, infectious vesico-rectal fistula caused by prior sigmoidectomy, prolonged bile leakage, or catheter-related issues. As a results, 85 of 95 patients received PIHP. The median OS of all 95 patients was 19 months and the overall survival rates at 1, 3 and 5 years were 70%, 28% and 21% respectively. The response rate of PIHP was approximately 70% (CR 23, PR 36, SD 15, PD 11). In 85 patients who completed reductive hepatectomy and PIHP, the median OS was 20 months and the overall survival rates at 1, 3 and 5 years were 73%, 35% and 24% respectively. Multivariate analysis indicated that tumor response to PIHP and normalization of serum DCP concentrations after PIHP were both independent prognostic factors for overall survival.

Conclusions: Reductive hepatectomy plus PIHP produced a high rate of tumor response with promising long-term survival in a subset of patients with advanced bilobar HCC. We believe the anti-tumor effect of the secondary treatment after reductive hepatectomy is the most vital part of this strategy.

Speaker's Curriculum Vitae

Name Pierce K.H. Chow, MBBS, M.Med (Surg), FRCSE, FAMS, PhD

Institution Senior Consultant Surgeon, Department of General Surgery, Singapore General Hospital; Visiting Consultant, National Cancer Centre; Professor, DUKE-NUS Graduate Medical School



Professor Pierce Chow is an academic surgeon and Professor at the Duke-NUS Graduate Medical School. He is concurrently Senior Consultant Surgeon at the National Cancer Centre Singapore (NCCS) and the Singapore General Hospital (SGH), and NMRC Senior Clinician Scientist. Professor Chow's interests are in oncology and the development of medical devices. He has successfully lead multi-disciplinary teams in translational oncology research and has been protocol chair of multi-national investigator-initiated clinical trials. He was conferred the 2012 NMRC National Outstanding Clinician Scientist Award for his research on Liver Cancer.

Professor Chow was the Chapter of Surgeon's Gold Medalist at the conjoint Royal College of Surgeons of Edinburgh/M.Med (Surgery) examination in 1994 and completed a clinical fellowship in Liver Transplantation in Australia in 2000. In 1995, he won the prestigious Young Surgeon's Award of the Academy of Medicine for his research into the patho-physiology of liver blood flow and regeneration. He has gone on to receive many other academic and professional awards. He has received 2 NMRC Research Fellowships (in 1995 and 1997) and in 2004 was conferred his PhD.

Professor Chow has published extensively on hepato-biliary cancers and gastrointestinal stromal tumours and carried out both preclinical and clinical research on brachytherapy in HCC and pancreatic cancers. He has more than 180 scientific papers, books and book chapters and advises both government and industry on biomedical research. He also has established a strong track record in experimental oncology and in clinical trials. He co-founded the Asia-Pacific Hepatocellular Carcinoma Trials Group in 1997 and has been the protocol chair of 5 multi-national trials. Currently, Professor Chow is the protocol chair of a 26-center investigator-initiated phase III trial that compares a selective internal radiation device (SIRsphere®) against molecular targeted therapy (sorafenib) in locally advanced HCC. The trial is funded jointly by both NMRC and industry and is conducted under the auspices of the Asia-Pacific Hepatocellular Carcinoma (AHCC) trials group. In 2012 he was conferred the National Outstanding Clinician-Scientist Award for his research on hepatocellular carcinoma.

SS05-3

The Impact of Microvascular Invasion on Surgical Outcomes in Hepatocellular Carcinoma

Pierce K.H. Chow

Duke-NUS Graduate Medical School, Singapore; National Cancer Center Singapore; Singapore General Hospital, Singapore

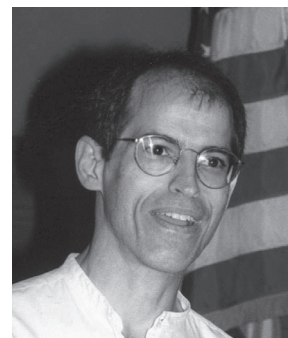
In spite of improvements in therapeutic approaches and the development of new modalities of treatment for Hepatocellular Carcinoma (HCC), surgical resection remains the main modality of treatment that confers consistent improved survival and potential cure to patients with HCC. It is currently the modality against which other therapies are compared.

Over the last 10 years, clinical outcomes with surgical resection has improved significantly with better patient selection, improved peri-operative care and the consolidation of expertise in academic surgical centers. The long-term survival of surgical resection for HCC are now a reflection of the under-lying HCC tumor burden at the time the patient underwent surgical resection, as well as biological factors intrinsic to the tumor in that patient. Detailed studies by our group and other have confirmed that the presence of microvascular invasion (MVI) results in significantly shorter time to tumor recurrence (TTR) as well as overall survival (OS). When matched for tumor burden as defined by the Milan Criteria, MVI, which is a reflection of tumor biology, has significantly greater impact on OS than tumor burden as defined by the Milan criteria. This has implications on the way the patients should be followed up and these patients would be the group most likely to benefit from clinical trials in adjuvant therapy.

When recurrence occurs, the group of patients with MCI is also more likely to first recur at extra-hepatic sites. This has major implications on liver transplantation. The results are discussed.

Speaker's Curriculum Vitae

Name Myron Eliot Schwartz, MD
Institution Mount Sinai School of Medicine



Academic Appointments:

7/02 Professor of Surgery, Mount Sinai School of Medicine, New York, N.Y.
12/93–6/02 Associate Professor of Surgery, Mount Sinai School of Medicine, New York, N.Y.
7/87–12/93 Assistant Professor of Surgery, Mount Sinai School of Medicine, New York, N.Y.
7/85–6/87 Instructor in Surgery, Mount Sinai School of Medicine, New York, N.Y.

Hospital Appointments:

7/12 Director of Liver Surgery, Recanati Miller Transplantation Institute
7/04 Director, Surgical Oncology, Associate Director, Liver Transplantation
7/02 Director, Adult Liver Transplantation and Hepatobiliary Surgery
1/99–6/02 Deputy Director, Liver Transplantation, Chief, Hepatobiliary Surgical Services
7/77–10/80 Director, Craigsville Medical Center, Craigsville, VA
7/87–6/89 Section Chief, Bronx Veterans Admin Hospital, Bronx, N.Y.
1/91–12/98 Associate Director, Division of Liver Transplantation
12/93 Associate Attending, Mount Sinai Hospital, New York, N.Y.
7/87–12/93 Assistant Attending, Mount Sinai Hospital, New York, N.Y.
1/78–10/80 Medical Examiner, Augusta County, VA
7/77–10/80 Attending Physician, Kings' Daughters' Hospital, Staunton, VA

Education:

1976 MD, Jefferson Medical College, Philadelphia, PA
1974 B.S. (Summa cum laude), Pennsylvania State University, State College, PA

Postdoctoral Training:

7/86–6/87 Fellow, Vascular Surgery, Mount Sinai Hospital, New York, N.Y.
7/85–6/86 Chief Resident, General Surgery, Mount Sinai Hospital, New York, N.Y.
7/81–6/85 Resident, General Surgery, Mount Sinai Hospital, New York, N.Y.
7/76–6/77 Rotating Internship, Mercy Catholic Medical Center, Darby, PA

Certification:

10/88 American Board of Surgery, Certified in General Vascular Surgery, ID# 100100
10/87 American Board of Surgery, Certified in General Surgery, ID# 32710

Licensure:

3/83 New York #146980
5/77 Virginia #29046

Honors and Awards:

1998 Physician of the Year Award, Transplant Recipients' International Organization
1986 Arthur Aufses Sr.; Prize in Surgery
1975 Alpha Omega Alpha; Medical Honor Society
2012 Doctorate Degree Honoris Causae; Favolaro University, Buenos Aires, Argentina

SS05-4

Liver Transplantation for Hepatocellular Carcinoma

Myron E. Schwartz

Mount Sinai School of Medicine, New York, NY, USA

Liver transplantation (OLT) is the treatment of choice for patients with unresectable early stage HCC, yielding posttransplant survival rates around 90% at one year and 75% at 5 years when the Milan criteria proposed by *Mazzaferro et al.* (solitary tumor ≤ 5 cm, or 2–3 nodules all <3 cm and without gross vascular invasion or extrahepatic spread) are employed as the basis for candidate selection. The applicability of liver transplantation is limited by the availability of donor organs, which varies considerably from one locale to another. Nonsurgical treatment of HCC while awaiting transplant has become routine to prevent tumor progression and drop-out from the waiting list. Expansion of selection criteria beyond Milan remains controversial, with down-staging (successful nonsurgical treatment of HCC to reduce tumor size and number to within Milan criteria, followed by a period of observation) the most commonly-used approach. Living donor transplantation is a useful alternative source of donor organs that can eliminate the risk of drop-out and enable transplant for patients with HCC that is modestly beyond Milan criteria.

Speaker's Curriculum Vitae

Name Shinji Uemoto
Institution Department of HBP Surgery and Transplantation, Kyoto University



Education:

Graduated from Kyoto University School of Medicine, March 1981

Graduated from Kyoto University Graduate School of Medicine, March 1990

Career:

- 1) Junior resident, Department of Surgery, Kyoto University Hospital: 1981
- 2) Senior resident, Tsukaguchi Hyogo Municipal Hospital: 1982–1986
- 3) Fellow, 2nd Department of Surgery, Kyoto University: 1990–1992
- 4) Assistant professor, 2nd Department of Surgery, Kyoto University: 1992–1996
- 5) Assistant professor, Department of Transplant Surgery, Kyoto University: 1999
- 6) Associate professor, Department of Transplant Surgery, Kyoto University: 2001
- 7) Professor and director, 1st Department of Surgery, Mie University: 2001–2006
- 8) Professor and director, Department of HPB Surgery and Transplantation, Kyoto University Graduate School of Medicine: 2006–present
- 9) Vice-director of Kyoto University Hospital: 2011–present

SS05-5

Hepatic Resection Versus Liver Transplantation for Hepatocellular Carcinoma: A Propensity Score Matching Study*Shinji Uemoto*

Department of HBP Surgery and Transplantation, Kyoto University, Japan

Background: The aim of this study is to compare the outcomes after hepatic resection (HR) with those after liver transplantation (LT) for hepatocellular carcinoma (HCC) between well-matched patient groups.

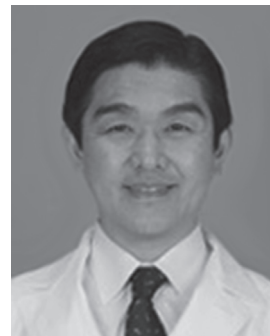
Methods: Between January 1999 and August 2012, 1062 patients (858 HR, 204 LT) underwent surgical therapy for HCC at our institute. Among these, the propensity-matched 80 patients comprised the propensity-matched cohort.

Results: The 1- and 5-year overall survival rates were 90% and 54% in the HR group and 82% and 63% in the LT group, respectively, which were not significantly different ($P = 0.613$). The 1- and 5-year recurrence rates in the LT group (9% and 21%) were significantly lower than those in the HR group (42% and 75%) ($P = 0.001$). Similar results were obtained in the propensity-matched 46 patients within our new expanded criteria for LT for HCC.

Conclusions: LT showed significantly lower recurrence rates compared with HR based on the propensity score matching study in the treatment of HCC, although survival rates did not differ between these treatments.

Speaker's Curriculum Vitae

Name Shuichiro Shiina, MD, PhD
Institution Professor,
Department of Gastroenterology,
Juntendo University



Education:

1982 MD, University of Tokyo, Faculty of Medicine

Professional Career:

2001–present: Visiting Professor, Wakayama Municipal College of Medicine, Wakayama
2012–Present: Professor, Department of Gastroenterology, Juntendo University
2004–2012: Associate Professor, Department of Gastroenterology, University of Tokyo
1997–2004: Assistant Professor, Department of Gastroenterology, University of Tokyo
1996–1997: Director, Department of Gastroenterology, Chigasaki Municipal Hospital, Kanagawa
1992–1996: Assistant Professor, Department of Medicine (II), University of Tokyo
1986–1992: Instructor, Department of Medicine (II), University of Tokyo
1983–1986: Resident in Medicine & Clinical Fellow in Gastroenterology, Mitsui Memorial Hospital, Tokyo
1982–1983: Resident in Medicine, University of Tokyo, Tokyo

Memberships:

The American Gastroenterological Association, Asian Pacific Association for the Study of the Liver, The International Liver Cancer Association (Founding member), The International Association of Pancreatology, The Japanese Society of Internal Medicine, The Japanese Society of Gastroenterology, The Japan Society of Hepatology, Japan Gastroenterological Endoscopy Society, The Japan Society of Ultrasonics in Medicine, The Japanese Society of Adult Diseases, The Liver Cancer Study Group of Japan, Study Group of Microwave Surgery, The Japan Society of Clinical Oncology, The Japan Pancreas Society, Japanese Society for Gastroenterological Carcinogenesis, Japan Association of Molecular Targeted Therapy for HCC, Japan Biliary Association, Japan Radiological Society.

Research Interests:

Interventional oncology and minimally invasive therapy, such as radiofrequency ablation, Diagnosis and treatment of liver neoplasms, Chemotherapy of GI tract cancers.

SS06-1

How to Obtain Sufficient Safety Margin in RFA? Japanese Standard

Shuichiro Shiina

Department of Gastroenterology, Juntendo University, Japan

Radiofrequency ablation (RFA) has been widely performed on patients with HCC, generally for those with Child-Pugh class A or B liver dysfunction who have three or fewer tumors each 3 cm or less in diameter. RCTs proved that RFA has superior overall survival to ethanol injection, because of better local control of the tumor. RFA had a 46% smaller risk of death (adjusted relative risk, 0.54 [95% CI: 0.33–0.89], $P = 0.02$), and an 88% smaller risk of local tumor progression (relative risk, 0.12 [95% CI: 0.03–0.55], $P = 0.006$) than ethanol injection (Shiina S, et al. Gastroenterology 2005).

In Japan, it is a common practice to perform an additional ablation when there are possible undestroyed tumor portions. We repeat ablations until contrast-enhanced CT or MRI shows entire tumor necrosis. In our over 10-year experience, in which we performed 2,982 RFA treatments on 1,170 primary HCC patients, final CT images showed complete tumor ablation in 2,964 (99.4%) of the 2,982 treatments. Five- and 10-year local tumor progression rates were both 3.2%, while 5- and 10-year distant recurrence rates were 74.8% and 80.8%, respectively (Shiina S, et al. Am J Gastroenterol 2012).

There is a strong argument in Japan that which is superior in the treatment of HCC, resection or ablation. Complete tumor necrosis is a requirement for RFA to be a treatment of choice in resectable HCC. To surely obtain entire tumor necrosis, it is necessary to ablate not only the tumor but also some amount of the surrounding liver parenchyma all around the tumor (safety margin). The concept of safety margin was first advocated in our histopathologic study of 18 HCC cases treated by ethanol injection. In 4 cases of incomplete necrosis, the viable cancer tissue remained in small tumor nodules around the main tumor, in portions isolated by septa, or along the edge of the tumor (Shiina S, et al. Cancer 1991).

If RFA definitely achieve entire tumor necrosis, RFA may be superior to surgical resection, because it is minimally invasive, and easily repeatable for recurrence.

Speaker's Curriculum Vitae

Name Riccardo Lencioni, MD, FSIR, EBIR
Institution Professor and Director,
Division of Diagnostic Imaging and
Intervention,
Pisa University School of Medicine



Riccardo Lencioni, MD, FSIR, EBIR, is board certified in Radiology and Gastroenterology. He is Professor and Director of Diagnostic Imaging and Intervention at Pisa University School of Medicine in Pisa, Italy.

Professor Lencioni is one of the world's foremost interventional oncology specialists, known especially for his highly influential work in liver cancer. He has been a leading member of several expert panels developing recommendations for research and clinical management of hepatocellular carcinoma. He has co-authored the white papers *Design and Endpoints in Clinical Trials in Hepatocellular Carcinoma* (2008), *Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma* (2010), and *EASL-EORTC Clinical Practice Guidelines: Management of Hepatocellular Carcinoma* (2012).

Riccardo Lencioni is the Chairman of the World Conference on Interventional Oncology. He is a co-Founder of the International Liver Cancer Association, in which he also acts as the Executive Secretary. He is an Associate Editor of the journal *Liver Cancer* and serves as an editorial board member or reviewer for several other titles.

Riccardo Lencioni has published 175 articles in peer-reviewed international journals indexed in PubMed and numerous chapters in textbooks of interventional radiology, gastroenterology, oncology and surgery. In addition, he has been the editor of seven books. According to the SCOPUS database, citations of his publications currently number in excess of 11,000 with an *h* index of 45. Riccardo Lencioni has been an invited or honorary lecturer at more than 450 international meetings or conferences.

SS06-2

Radiofrequency Ablation: Western Standard

Riccardo Lencioni

Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy

In the West, image-guided radiofrequency ablation (RFA) is widely accepted as the most appropriate therapeutic choice for patients with early-stage hepatocellular carcinoma (HCC) when surgical options – including resection and transplantation – are precluded. RFA has shown superior anticancer effect and greater survival benefit with respect to the seminal percutaneous technique, ethanol injection, in meta-analyses of randomized controlled trials, and is currently established as the standard ablative modality. An open question is whether RFA can compete with surgical resection as first-line treatment. Randomized controlled trials completed so far failed to provide an unequivocal answer. Uncontrolled investigations have also reported similar results for resection and RFA in very early stage tumors – ie, single HCC smaller than or equal to 2 cm in diameter. Caution, however, is needed when interpreting and generalizing these results, in particular in the light of studies that suggest a non-negligible rate of incomplete pathologic response after RFA. Western studies performed in liver specimens of patients who underwent RFA as bridge treatment to transplantation showed that tumor size greater than 3 cm in diameter and presence of large (3 mm or more) abutting vessels result in a drop of the rate of complete tumor eradication to less than 50%. Is a standard RFA still the best technique for tumor ablation in 2014? Several novel thermal and non-thermal techniques for tumor ablation – including microwave ablation and irreversible electroporation – seem to offer potential advantages over RFA and are currently undergoing clinical investigation. Advances in ablation systems and devices are highly warranted. However, progress in imaging guidance and monitoring is also key to success. To be able to compete with surgical resection, image-guided ablation needs to be able to offer more accurate prediction of the outcome of the procedure in each individual patient. Variability in outcomes needs to be minimized via careful treatment planning. Also, the outcome of the ablation procedure needs to be carefully documented by providing evidence that an “A0” treatment has been achieved.

Speaker's Curriculum Vitae

Name Shi-Ming Lin
Institution Division of Hepatology,
Department of Gastroenterology
and Hepatology, Chang Gung
Memorial Hospital,
Chang Gung University



Education:

College of Medicine, National Taiwan University, Taipei

Current Positions:

Professor and Chief, Division of Hepatology, Chang Gung Memorial Hospital, LinKuo and Taipei

Founding President, Taiwan Academy of Tumor Ablation

Hosting Chairman, 1st Asian Conference on Tumor Ablation, Taipei, 2014

Professional Experiences:

Dr. Lin is one of the pioneers of RFA for liver tumors in Taiwan; His research interest focused on antiviral treatment for hepatitis B, local ablation for HCC and tertiary prevention of HCC recurrence. Dr. Lin has published 96 papers in international and domestic scientific journals including Gastroenterology, Hepatology, Gut, Journal of Hepatology, Cancer, and British Journal of Surgery. Dr. Lin has 4 papers (published in Hepatology 1999 and Gastroenterology 2004, Gut 2005 and J Hepato 2007) ranked as the highly cited papers. Dr. Lin has given 103 invited lectures in the area of his expertise on occasions to international audiences including APASL (2006, 2008–9, 2012, 2013), APDW (2007, 09), Annual Microwave Surg Meeting Jpn (2008, 09), Kobe HCC symposium (2009), APPLE (2010–2013), 2013 Korea-Japan Image-guide Tumor Ablation Meeting, Japan JSH 2012, HK IDD 2011, HK Interventional Radiology Symposium 2009, South East Asian Nations conference (2008, 2010, 2012), and Singapore GI Annual Meeting 2009, Asian Congress of Tumor Ablation (ACTA) 2014, and 4th International Kyoto Liver Cancer Symposium 2014. Dr. Lin is serving as a journal referee of many peer-review journals including Gastroenterology, Hepatology, Gut, J Hepatol, Ann Surg, Cancer Treatments Reviews, PLoS ONE, Future Oncology, J Surg Oncol, J Translational Med, Cancer Investig, Europ J Gastroenterol Hepatol, Dig Liver Dis, Cytokine, JGH, and Liver International.

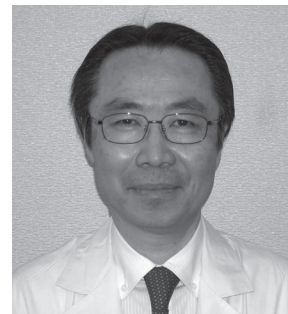
SS06-3**How to Obtain Sufficient Safety Margin in RFA?****Taiwan Standard***Shi-Ming Lin*

Division of Hepatology, Department of Gastroenterology and
Hepatology, Chang Gung Memorial Hospital, Taipei and Linkou,
Chang Gung University, Taoyuan, Taiwan

The extent of safety margin after RFA is strongly correlated with local tumor progression (LTP). However, so far only a few studies have reported this issue and there is no standard definition of safety margin for HCC after RFA in Taiwan. Therefore, we aim to examine the relationship between our previously proposed grading system related to the ablative margin after RFA and clinical outcomes. This retrospective study recruited patients with treatment-naïve HCC undergoing RFA between July 2013 and December 2013 in Chang Gung Memorial Hospital, Linkou. Complete ablation was diagnosed by dynamic CT. Recurrent nodules were classified according to hyperattenuation in the arterial phase on CT. There were 42 patients (61.9% male, mean age 70.1 years) were newly diagnosed with single HCC and 9 patients of them had recurrent HCC (6 local tumor progression, 3 additional new recurrence) after successful RFA. There is no relation between LTP and various parameters including age, gender, etiology of liver disease, cirrhosis, tumor size, BCLC stage 0 vs. A, prior treatment, tumor location. Uni-variate analysis in LTP only showed higher baseline AFP level (115 in LTP group vs. 6.8 ng/ml in LTP-free group, $p = 0.010$) and installation of intra-peritoneal or intra-pleural fluid (83% in LTP group vs. 27.8% in LTP-free group, $p = 0.016$) were associated with higher LTP. However, multivariate analysis showed that LTP was marginally inversely associated with safety margin >5 mm (HR 0.135, 95% CI: 0.02–1.22, $P = 0.074$). Total recurrence of HCC was significantly inversely associated with safety margin >5 mm (HR 0.025, 95% CI: 0.002–0.272, $p = 0.002$). In conclusion, safety margin <5 mm in HCC after RFA is an independent predictor of recurrent HCC after successful RFA. Further studies with larger populations are required to validate our findings.

Speaker's Curriculum Vitae

Name Yasuharu Imai, MD, PhD
Institution Department of Gastroenterology,
Ikeda Municipal Hospital



Yasuharu Imai, MD, PhD is currently President of Ikeda Municipal Hospital is also Visiting Professor of Osaka University School of Medicine. He graduated from Osaka University School of Medicine in 1978. He went on to become Assistant Professor of the 2nd Department of Medicine at the Osaka University Graduate School of Medicine for thirteen years. He was also a research fellow at the Royal Free Hospital School of medicine in London. He is widely published and sits on the reviewer board for a number of journals. His special interest includes imaging diagnosis, treatment and prevention of hepatocellular carcinoma.

1978	Graduated from Osaka University School of Medicine
1980–1993	Fellow, Assistant Professor of 2 nd Dpt. of Internal Medicine Osaka University Graduate School of Medicine
1988–1990	Research fellow, Royal Free Hospital School of Medicine, University of London
1993–2005	Chief, Dpt. Of Gastroenterology, Ikeda Municipal Hospital
2008–	Visiting Professor of Gastroenterology, Osaka University School of Medicine
2006–	Vice President, Ikeda Municipal Hospital
2013–	President, Ikeda Municipal Hospital

Award:

European Radiology – Most Cited Paper 2010 award
Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. Eur Radiol 2010;20:2405–13.

Specialty:

Imaging diagnosis, treatment and prevention of hepatocellular carcinoma, Treatment of viral hepatitis.

SS06-4

Extracted-Overlay Function in Volume Navigation System for the Treatment and Evaluation of Radiofrequency Ablation for Hepatocellular Carcinoma

Yasuharu Imai¹, Takumi Igura¹, Yoshiyuki Sawai¹, Sachiyo Kogita¹, Kazuto Fukuda¹, Yuki Makino², Takamichi Murakami³

¹Department of Gastroenterology, Ikeda Municipal Hospital, Japan;

²Department of Gastroenterology and Hepatology, Osaka University

School of Medicine, Japan; ³Department of Radiology, Kinki University School of Medicine, Japan

Background: CT/MR-US fusion imaging system has been reported to be useful for radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC). Recently, we developed a novel technique, Extracted-overlay function, in which only an extracted tumor together with a virtual safety ablative margin of arbitrary thickness around the tumor such as 5 mm is overlaid on US, and investigated its usefulness for the treatment and evaluation of RFA for HCC using Volume Navigation system (GE Healthcare).

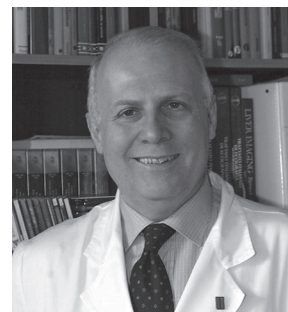
Methods: Ninety HCCs treated by RFA with this function were included. For Extracted-overlay function, after CT or MR imaging data used as a reference were imported into Advantage Workstation Volumeshare 4 (GE Healthcare), a target tumor was extracted from original data and ablative safety margin was added to the tumor. These image data were imported into LOGIQ E9 (GE Healthcare) equipped with Volume Navigation system and overlaid on US images, after registration of US and reference images. In RFA, an electrode was inserted targeting the overlaid tumor and margin. After ablation, contrast-enhanced US (CEUS) was conducted for treatment evaluation and an ablative margin was categorized into 3 groups; (I) <0 mm (protruding from ablation zone), (II) 0 to <5 mm, and (III) ≥5 mm. The categorization of an ablative margin was compared between CEUS and fusion imaging of pre- and post-RFA CT or MRI, which was reported to enable accurate treatment evaluation of RFA.

Results: The number of HCCs in groups I, II, and III on CEUS was 3, 73, and 8, respectively, and the other 6 HCCs were located too deep to evaluate. On CT or MR fusion imaging, the number of HCCs in groups I, II, and III was 10, 73, and 6, respectively. In 80 HCCs (88.9%), the categorization agreed between CEUS and fusion imaging and the overall agreement was moderate (κ coefficient 0.47, moderate agreement). Among 81 HCCs judged as complete ablation (groups II or III) on CEUS, complete ablation was also confirmed in 77 HCCs (95.0%) on CT/MR fusion imaging.

Conclusions: Extracted-overlay function enables effective treatment planning. Since a target tumor and virtual ablative margin remain visible even during and after ablation, it enables noninvasive and quantitative treatment evaluation at the bedside just after RFA, by combining with CEUS.

Speaker's Curriculum Vitae

Name Luigi Bolondi
Institution Department of Digestive Diseases
and Internal Medicine; Alma Mater
Studiorum, University of Bologna



Academic Career:

Full Professor of Internal Medicine at the University of Bologna Italy
Chairman of the Department of Digestive Disease and Internal Medicine,
University Hospital, Bologna Italy
Director of the PhD course in Medical Sciences at the University of Bologna
(2006–2012)
Director of the Centre of Applied Biomedical Research at the University of
Bologna
President of the School of Medicine University of Bologna (2012–2015)

Publications:

3 international Textbooks
301 full articles on international Journals cited on Medline
55 chapters on international textbooks.
Impact Factor > 1160 H Index = 57

Editorial Activity:

He served as a Member of the Editorial Board of "Hepatology" (1993–96) "Journal
of Clinical Ultrasound", Journal of Hepatology" (until 2005) and as Associate
Editor of "European Journal of Ultrasound" (until 1999)
He is now Associate Editor of Journal of Hepatology (starting April 2014)

Activity in Scientific Societies:

General Secretary (1981–1989) and President (1993–95) of the Italian Society
for Ultrasound in Medicine and Biology
Member of the board of the Italian Society for the Study of the Liver (1993–96)
Honorary Member of the American Institute of Ultrasound in Medicine (AIUM)
President of the European Federation of Societies of Ultrasound in Medicine and
Biology (1996–1999)
He has organized 4 national Congresses of the Italian Society for Ultrasound in
Medicine and Biology between 1981 and 1994
He has organized the EASL single topic meeting on HCC in 2000
He has organized the World Congress of Ultrasound in Medicine and Biology of
2000
He has been Chairman of the European Congress for Ultrasound in Medicine and
Biology in Bologna 2006

SS07-1

Heterogeneity of Intermediate HCC

Luigi Bolondi

Department of Digestive Diseases and Internal Medicine; Policlinico
S. Orsola Malpighi – Alma Mater Studiorum, University of Bologna, Italy

Patients classified as having intermediate HCC by the Barcelona Clinic Liver Cancer (BCLC) staging system present with varying tumor burden and liver function and therefore represent unique challenges for therapeutic management, different from the early and advanced stages. Transarterial chemoembolization (TACE) is currently recommended by EASL and AASLD guidelines as standard of care in this setting, but there is considerable variation in the clinical benefit patients derive from this treatment.

This heterogeneous group consists of patients with Child–Pugh A and B liver function with large/multifocal HCC, defined as >3 tumors regardless of size, or 2–3 tumors >3 cm in maximal diameter, or one single unresectable tumor >5 cm, in the absence of cancer-related symptoms, macrovascular invasion or extra-hepatic spread. Apart from the large ranges of tumor burdens and grades of functional impairments which belong to this stage, a major limitation relies in the subjective definition of the Performance Status (PS) on the basis of the ECOG classification and the possible overlap of PS0 and PS1. Furthermore, in patients with lack of definite demonstration of the nature of the thrombosis or very limited peripheral neoplastic portal vein thrombosis, the boundaries between intermediate and advanced HCC are further blurred.

Several guidelines for the management of HCC, including NCCN, JSH, and APASL recognize the heterogeneity of patients with intermediate HCC and the lack of evidence supporting a single treatment approach to address the needs of all these patients. These guidelines endorse alternative treatment options for different subgroups of patients within the general category of intermediate HCC.

To facilitate clinical decisions it is necessary to distinguish major from minor tumor burden, which would influence the allocation of patients to TACE/TAE or to alternative treatments (e.g. radioembolization, transplantation or sorafenib). For this purpose we suggested the ‘up to 7’ criterion. This criterion combines the number of nodules and the size of the largest tumor, with the sum being no more than 7. Regarding liver function, subgroups within intermediate stage may be defined by Child–Pugh score and class, clinical jaundice (usually corresponding to total bilirubin concentration of approximately >2.5 mg/dL/42.5 mmol/L) and the presence or absence of clinical ascites. Possible presence of peripheral/(sub)segmental portal vein thrombosis has been added as a further discrimination criterion.

Taking into account these points, we (ref) proposed four subgroups for patients within the intermediate BCLC B stage. These proposed subgroups are linked to different first-line and alternative treatment options.

Reference:

Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma; proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012;32:348–359.

Speaker's Curriculum Vitae

Name Hiroaki Nagano, MD, PhD
Institution Department of Surgery and Transplantation Medicine, Osaka University Hospital



Educations:
1986 Passed the examination of National Board
1986–1987 Junior Resident, Department of Surgery II, Osaka University Hospital
1987–1990 Resident, Department of Surgery, The Center for Cancer and Cardiovascular Diseases of Osaka
1990–1994 Surgical Staff, Department of Surgery II, Osaka University Hospital
1994–1997 Research Fellow, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School
1997–2004 Assistant Professor, Department of Surgery, Graduate School of Medicine, Osaka University
2004–2009 Associate Professor, Department of Surgery, Graduate School of Medicine, Osaka University
2010–present Professor, Department of Surgery and Transplantation Medicine, Osaka University Hospital

Speciality & Research Field of Interest:

Hepatobiliary-pancreatic Surgery and Liver Transplantation
Hepatobiliary-pancreatic Cancer, Transplant Immunology

Recent Selected Publications:

1. [Nagano H](#), Tomimaru Y, et al. Int J Oncol 2013;43(4):1066–1072.
2. [Nagano H](#), Ishii H, et al. Journal of Hepato-Biliary-Pancreatic Science 2012;19(6):600–605.
3. Tomimaru Y, [Nagano H](#), et al. Int J Cancer 2012;130(2):319–327.
4. Tanemura M, [Nagano H](#), et al. Am J of Transplantation 2012;12(1):102–114.
5. [Nagano H](#), Wada H, et al. Oncology 2011;80(1–2):63–69.
6. Nakamura M, [Nagano H](#), et al. Cancer 2008;112(8):1765–1771.
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9. [Nagano H](#), Sakon M, et al. Hepatogastroenterology 2007;54(73):172–179.
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13. [Marubashi S](#), [Nagano H](#), et al. Transplantation 2005;80(12):1671–1675.
14. Kondo M, [Nagano H](#), et al. Clin Cancer Res 2005;11(3):1277–1286.
15. Yamamoto T, [Nagano H](#), et al. Clin Cancer Res 2004;10(23):7884–7895.

Membership of Academic Society:

Transplantation Society
Japan Surgical Society
Japanese Society of Gastroenterological Surgery
Japanese Society of Clinical Surgery
Japanese Association of Hepato-Biliary-Pancreat Surgery
Japanese Society for Transplantation
Japanese Society of Gastroenterology
Japanese Society of Hepatology
Japanese Society of Cancer Therapy

SS07-2**Surgical Treatment for Intermediate Stage HCC***Hiroaki Nagano*Department of Surgery and Transplantation Medicine, Osaka University
Hospital, Japan

Current guidelines recommend transarterial chemoembolization (TACE) as the standard treatment of intermediate stage (BCLC-B) HCC patients. However, despite several recent advances and technical refinements, the long-term survival outcomes of patients managed with this technique do not appear fully satisfactory; in addition, intermediate-stage HCC includes a heterogeneous population of patients with varying tumour burdens, liver function and disease a etiology. In this symposium, I will present about the possibility of surgical treatment for intermediate stage (BCLC-B) HCC.

Speaker's Curriculum Vitae

Name Osamu Matsui
Institution Department of Advanced Medical
Imaging, Kanazawa University
Graduate School of Medical
Sciences



Dr. Osamu Matsui is a graduate of Kanazawa University Faculty of Medicine in 1972 and completed radiology residency at Kanazawa University hospital. He was promoted to full professor and chairman for the Department of Radiology, Kanazawa University in 1999. In 2010, he was appointed for the dean of Kanazawa University Graduate School of Medical Science, and is now the specially appointed research professor of the Department of Advanced Medical Imaging and professor of emeritus at the same institute. His main clinical and research contributions have been in the diagnostic imaging and interventional radiology, especially for liver cancer. He is now an associate editor of gastrointestinal section of Radiology. He was selected one of the distinguished scientists of Japan in 2009 by the Minister of Education, Culture, Sports, Science and Technology.

SS07-3**Superselective (Subsegmental) Lipiodol TACE***Osamu Matsui¹, Shiro Miyayama²*¹Department of Advanced Medical Imaging, Kanazawa University Graduate School of Medical Sciences, Japan; ²Department of Radiology, Fukui Saiseikai Hospital, Japan

In Japan, since mid-1990, superselective (segmental, subsegmental, ultraselective) TACE with a mixture of anticancer drugs and Lipiodol (iodized oil) followed by gelatin particles using microcatheter system has been the standard technique. Because Lipiodol is semi-fluid, and it can flow into the surrounding portal venules and hepatic sinusoids through peribiliary plexus (PBP) and through the drainage route from the hypervascular HCC, resulting in strong ischemic effect. Reported CR ratios in definitely hypervascular HCCs were around 30–60% for ≤ 5 cm. In addition, when analysis was restricted in the patients with HCCs ≤ 5 cm and ≤ 3 in number, around 50% of 5 yr survival rate was reported by many authors. Therefore, RCT had been ethically difficult in Japan. However, because of remarkable heterogeneity of the tumor burden in intermediate HCCs, overall 5 yr survival rate of the whole intermediate stage HCCs was around 25% according to the nation-wide survey. Yamakado et al recently conducted a subgroup analysis of intermediate HCCs, and found that the survival ratio was significantly different between the patients with HCC ≤ 4 tumors ≤ 7 cm and those with beyond them (JJR in press). Theoretically, superselective Lipiodol TACE is more effective in localized intermediate HCCs. Therefore, reevaluation of the efficacy of Lipiodol TACE in more advanced stage of intermediate HCCs is considered to be necessary in comparison with drug-eluting beads TACE, intra-arterial infusion chemotherapy and/or sorafenib therapy.

Speaker's Curriculum Vitae

Name Riccardo Lencioni, MD, FSIR, EBIR
Institution Professor and Director,
Division of Diagnostic Imaging and
Intervention, Pisa University
School of Medicine



Riccardo Lencioni, MD, FSIR, EBIR, is board certified in Radiology and Gastroenterology. He is Professor and Director of Diagnostic Imaging and Intervention at Pisa University School of Medicine in Pisa, Italy.

Professor Lencioni is one of the world's foremost interventional oncology specialists, known especially for his highly influential work in liver cancer. He has been a leading member of several expert panels developing recommendations for research and clinical management of hepatocellular carcinoma. He has co-authored the white papers *Design and Endpoints in Clinical Trials in Hepatocellular Carcinoma* (2008), *Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma* (2010), and *EASL-EORTC Clinical Practice Guidelines: Management of Hepatocellular Carcinoma* (2012).

Riccardo Lencioni is the Chairman of the World Conference on Interventional Oncology. He is a co-Founder of the International Liver Cancer Association, in which he also acts as the Executive Secretary. He is an Associate Editor of the journal *Liver Cancer* and serves as an editorial board member or reviewer for several other titles.

Riccardo Lencioni has published 175 articles in peer-reviewed international journals indexed in PubMed and numerous chapters in textbooks of interventional radiology, gastroenterology, oncology and surgery. In addition, he has been the editor of seven books. According to the SCOPUS database, citations of his publications currently number in excess of 11,000 with an *h* index of 45. Riccardo Lencioni has been an invited or honorary lecturer at more than 450 international meetings or conferences.

SS07-4

Transarterial Chemoembolization with Drug Eluting Beads

Riccardo Lencioni

Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy

Transarterial chemoembolization (TACE) has been established by a meta-analysis of randomized controlled trials as the standard of care for nonsurgical patients presenting with large or multinodular noninvasive tumor isolated to the liver and preserved liver function. TACE is also used in patients with early-stage HCC when curative therapies – including liver transplantation, hepatic resection, and image-guided ablation – are precluded. The ideal TACE scheme should allow maximum and sustained concentration of the chemotherapeutic drug within the tumor with minimal systemic exposure combined with calibrated tumor vessel obstruction. While conventional TACE with administration of an anticancer-in-oil emulsion followed by embolic agents has been the most popular technique, the introduction of embolic, drug-eluting beads has provided an alternative to Lipiodol-based regimens. Experimental studies have shown that TACE with drug-eluting beads has a safe pharmacokinetic profile and results in effective tumor killing in animal models. Early clinical experiences have confirmed that drug-eluting beads provide a combined ischemic and cytotoxic effect locally with low systemic toxic exposure. The clinical value of a TACE protocol performed by using the embolic microsphere DC Bead (Biocompatibles, UK) loaded with doxorubicin (DEBDOX; drug-eluting bead doxorubicin) has been shown by randomized controlled trials. In particular, in a multicenter study including 201 European patients (“PRECISION V”), use of DEBDOX resulted in a significant reduction in liver toxicity and drug-related adverse events compared with conventional TACE with Lipiodol and doxorubicin. Two other trials reported higher rates of tumor response and longer time-to-progression for the loaded DC Bead as compared to a bland embolic microsphere with similar characteristics. As a result of these investigations, DEBDOX has been increasingly used as the first-line transcatheter treatment for intermediate-stage HCC. Further randomized controlled studies are warranted to understand the applicability of these findings to patients at different stages of disease.

Speaker's Curriculum Vitae

Name Riccardo Lencioni, MD, FSIR, EBIR
Institution Professor and Director,
Division of Diagnostic Imaging and
Intervention, Pisa University
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Riccardo Lencioni, MD, FSIR, EBIR, is board certified in Radiology and Gastroenterology. He is Professor and Director of Diagnostic Imaging and Intervention at Pisa University School of Medicine in Pisa, Italy.

Professor Lencioni is one of the world's foremost interventional oncology specialists, known especially for his highly influential work in liver cancer. He has been a leading member of several expert panels developing recommendations for research and clinical management of hepatocellular carcinoma. He has co-authored the white papers *Design and Endpoints in Clinical Trials in Hepatocellular Carcinoma* (2008), *Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma* (2010), and *EASL-EORTC Clinical Practice Guidelines: Management of Hepatocellular Carcinoma* (2012).

Riccardo Lencioni is the Chairman of the World Conference on Interventional Oncology. He is a co-Founder of the International Liver Cancer Association, in which he also acts as the Executive Secretary. He is an Associate Editor of the journal *Liver Cancer* and serves as an editorial board member or reviewer for several other titles.

Riccardo Lencioni has published 175 articles in peer-reviewed international journals indexed in PubMed and numerous chapters in textbooks of interventional radiology, gastroenterology, oncology and surgery. In addition, he has been the editor of seven books. According to the SCOPUS database, citations of his publications currently number in excess of 11,000 with an *h* index of 45. Riccardo Lencioni has been an invited or honorary lecturer at more than 450 international meetings or conferences.

SS07-5

Drug Eluting Bead Chemoembolization Combined with Sorafenib

Riccardo Lencioni

Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy

Transcatheter arterial chemoembolization (TACE) is the current standard of care for patients presenting with intermediate-stage hepatocellular carcinoma (HCC). Despite the advances and refinements in TACE technique, the long-term survival outcomes of patients managed with TACE are not fully satisfactory, mainly as a result of the high rates of tumor recurrence. TACE exerts therapeutic effects only in the treated territory; thus, other areas of tumors – undetected at the time of the procedure – may progress, or new tumors may develop. Moreover, by interrupting blood flow to the tumor, TACE induces necrosis at the tumor site, but may create conditions that permit or encourage angiogenesis. Surrogate markers of tissue hypoxia that increase after TACE include hypoxia-inducible factor 1 alpha and both plasma and hepatic vascular endothelial growth factor (VEGF). Thus, inhibition of angiogenesis may be synergistic with TACE in patients with HCC. The introduction of molecular targeted agents that inhibit tumor cell proliferation and angiogenesis to the therapeutic armamentarium for HCC has prompted the design of clinical trials aimed at investigating the synergies between loco-regional and systemic treatments. The combination of TACE with agents with anti-angiogenic properties is appealing, since the systemically-active drug might curtail the post-TACE rise in VEGF-mediated signaling and at the same time target any tumor foci distant from the site of TACE. The availability of the drug eluting bead (DEB), that ensures a minimal systemic exposure to the chemotherapeutic agent at the time of the TACE, is appealing for concurrent combination regimens. Encouraging safety and efficacy signals were captured by the phase II studies completed so far. In particular, in the randomized, double-blind, placebo-controlled SPACE study (Sorafenib or Placebo in Combination with DEB-TACE for Intermediate-Stage HCC), the hazard ratio of the DEB-TACE plus sorafenib arm for time-to-progression, the primary endpoint, was 0.797 (95% CI, 0.588, 1.080; $p = 0.072$). Further randomized controlled studies are required to understand the correlation between these findings and overall survival benefit.

Speaker's Curriculum Vitae

Name Jean-Luc Raoul
Institution Institut Paoli-Calmettes, Marseille, France



Jean-Luc Raoul is Hepato-Gastroenterologist and Medical Oncologist ; he is currently Head of the Gastrointestinal Unit at the Comprehensive Cancer Center, Paoli-Calmettes Institute, Marseille, France.

He has held the position of Professor of Medical Oncology at Rennes University since 2000, and in 2005 he was appointed Visiting Professor at the University of Perth-Fremantle, Western Australia. He received his medical degree from Rennes University in 1986, following training at Brest , Rennes, and Paris. He then undertook studies at Paris VII University, Paris, and Rennes University, achieving certification in Hepato-Gastroenterology in 1988 and completing his PhD in 1996.

Professor Raoul has clinical and research interests in gastrointestinal cancers, oesophageal cancer and hepatocellular carcinoma, in particular the application of targeted internal radiation therapy and targeted therapies in this disease. He is a member of several societies (ASCO, ILCA, EASL, ESMO, AFEF, ...). He has published numerous articles, particularly in the field of hepatocellular carcinoma.

SS08-1

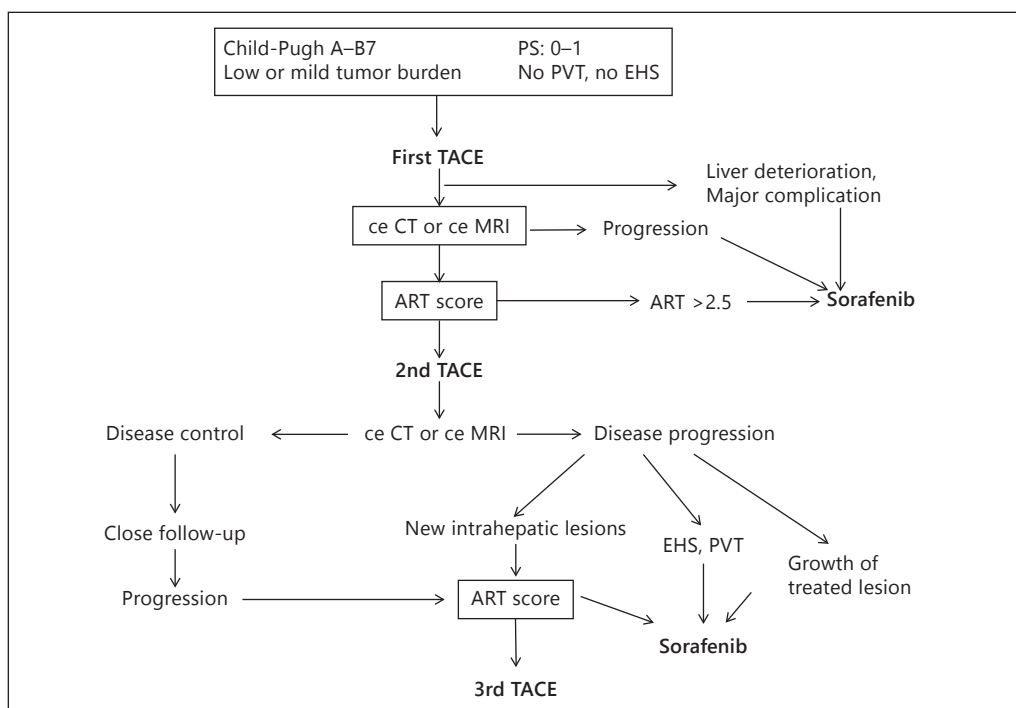
How to Define TACE Refractoriness: EASL Definition

Jean-Luc Raoul

Paoli-Calmettes Institute, Marseille, France

In Europe, trans-arterial chemoembolization (TACE) is usually given to intermediate stages following the BCLC staging system, and is associated with a modest improvement in median overall survival (+4 months from 16 mo to 20 mo). A novel drug delivery system (DC Beads) loaded with doxorubicin have shown similar efficacy but better tolerance than conventional TACE; moreover this technique seems reproducible and is mandatory in future randomized trials. But stopping rules for TACE are not well known because we do not have clear definition of TACE refractoriness or failure and this is a burning question as we now have a second line treatment for these patients, sorafenib (concept of treatment stage migration). Then European guidelines for TACE refractoriness/failure are based on previous trials failures and to the concept of unTACEable progression. Are considered as unTACEable progression: major local progression, extrahepatic spread, vascular invasion, worsening of liver function (>Child B7) and impaired performance status (>PS 1). Recently a new tool, the ART score has been defined selecting patients that will not benefit from a second TACE; this score, calculated just before the planned second TACE associates 3 parameters (increase in AST >25%, increase in Child-Pugh score, absence of tumor response) and allow to select a subpopulation with a very poor outcome that will not benefit from a second TACE. This score is also useful before the third and fourth TACE session. By contrast, tumor progression occurring a long time after the first TACEs or appearance of new lesions without vein thrombosis in a patients with a good performance status and a good liver function will require new TACE sessions.

In this presentation we will propose a new algorithm (Fig) based on the previously published data associated with the new ART score.



Speaker's Curriculum Vitae

Name Joong-Won Park
Institution Principal Scientist, Center for Liver Cancer, National Cancer Center, Korea



Joong-Won Park is a Principal Scientist of the National Cancer Center, Korea. He was the Head of the Center for Liver Cancer, NCC, Korea from 2002 to 2010, and was the Head of Translational and Clinical Research at the National Cancer Center Research Institute from 2008 to 2011. Dr. Park completed his Medical degree at Seoul National University in 1984 followed by a residency in Internal Medicine and a Clinical Fellowship in Hepatology at Seoul National University Hospital. He completed a PhD in Medicine at Seoul National University in 1996. He was an Assistant and Associate Professor of Chung-Ang University Medical College from 1993 to 2002 and was a Visiting Scientist at the Center for Basic Research in Digestive Diseases, Mayo Clinic, Rochester, USA, from 1997 to 1999. Dr. Park has published extensively in both International and Korean journals and given many invited lectures on hepatitis and liver cancer. He serves as Chair of the Committee for the Hepatocellular Carcinoma Management Guidelines of the Korea Liver Cancer Study Group (KLCSG)-NCC Korea and is a member of the Korean Association for the Study of the Liver (KASL), the Asian-Pacific Association for the Study of the Liver (APASL), the American Association for the Study of Liver Diseases (AASLD), and the International Liver Cancer Association (ILCA). He served as Chair of the Scientific Committee for the APASL 2008 Seoul meeting, a Chair of the Scientific Committee of the KASL from 2003 to 2005, and as Chair of the Scientific Committee of the KLCSG from 2002 to 2004. Dr. Park's research interests are the management of hepatocellular carcinoma, molecularly targeted therapy, and hepatocarcinogenesis.

SS08-2

How to Define TACE Failure/Refractoriness?: Korean Perspective

Joong-Won Park

Center for Liver Cancer, National Cancer Center, Korea

Randomized controlled trials have reported that transarterial chemoembolization (TACE) improved survival of selected patients with unresectable hepatocellular carcinoma (HCC). TACE has been recommended as a treatment of choice for patients with HCC of intermediate stage or Barcelona Clinic Liver Cancer (BCLC) stage B. However, the global HCC BRIDGE study, which was the first longitudinal cohort study to document the HCC patient from diagnosis to death, showed the difference between the recommendations and the real-world practice; TACE was the treatment most frequently used first in the most countries across all disease stages.

Because remaining, progressing or recurring tumors (RPRT) after first treatment is frequent in patients with HCC, second treatment and following treatment were important for the management of HCC. Following TACE, about one third of patients show a sustained response at 3–6 months, with 85% experiencing progression during long-term follow-up. The most common second treatment was TACE after first-line TACE in the recent cohort of National Cancer Center, Korea. Unfortunately, there are few studies about second treatment for the RPRT in HCC patients. Existing guidelines do not address the criteria for repeating TACE and recommendations about the number of TACE cycles to be repeated before switching to another or no treatment. This latter point relates to the criteria used to determine when to stop TACE treatments, either because TACE is now contraindicated, or because TACE is no longer effective in controlling the disease, referred to generally as TACE failure/refractoriness.

The recent proposal of ‘stage progression’ from Korea is potentially a useful concept and may provide a surrogate end-point for TACE refractoriness. By evaluating 264 patients with intermediate-stage HCC who underwent TACE and designating the development of vascular invasion or extrahepatic spread during follow up as stage progression (SP), the authors classified the patients according to disease course as: no progressive disease, PD without SP, PD followed by SP, and simultaneous PD and SP. Patients without SP (including both patients with no PD and those with PD but no SP) showed no difference in overall survival (36.6 and 35.8 months, respectively), patients with PD followed by SP had intermediate overall survival (23.9 months) and patients with simultaneous PD and SP had the worst overall survival (12 months). Multivariate analyses of OS indicated corresponding hazard ratios for each patient group. By classifying SP as new vascular invasion or extrahepatic spread, which includes radiologic progression of stage from BCLC stage B to stage C, the time from initial treatment to this point can be referred to as “time-to-stage progression” (TTSP). A further variation of this concept to accommodate the increasing number of cases of SP that develop as the duration of follow up increases has been proposed as ‘SP-free survival’. The authors contend this provides a composite end-point instead of TTSP which may indicate TACE-refractory HCC. Subsequent analysis indicated that the development of progression during the first 6 months from the initial TACE and the need for three sessions of TACE during the first 6 months were both associated with shorter SP-free survival and thus, TACE-refractory HCC. Stage progression, defined as the development of vascular invasion or extrahepatic spread during follow up, may provide a useful surrogate measure of TACE refractoriness although there is currently limited data regarding this.

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5. Kim YI, Park JW, Kim BH, et al: Clinical outcomes of second-recorded treatment in patients with recurrence or progression of hepatocellular carcinoma after initial treatment. *ILCA* 2013;Abstr. P-203.

Speaker's Curriculum Vitae

Name Markus Peck-Radosavljevic
Institution Associate Professor of Medicine,
Medical University of Vienna,
Vienna, Austria



Professor Markus Peck-Radosavljevic, MD is Associate Professor of Medicine and Vice-Chairman at the Department of Gastroenterology and Hepatology at the Medical University of Vienna, Austria.

Professor Peck has served as Vice-secretary of EASL from 2011 to 2013 and is currently Secretary General of EASL since April 2013. He also serves as the Secretary General of the Austrian Association for Internal Medicine.

He began his research in liver disease by investigating into the complications of portal hypertension and cirrhosis, initially mostly on hematologic problems in advanced stage liver disease, later also into bleeding complications. He has been actively involved into the liver transplant program, in particular regarding treatment of post-OLT hepatitis C. Later, he started to work on HCV-infection in hemodialysis patients and HIV-HCV coinfection.

Over the last few years, Professor Peck has been leading the Portal Hypertension, the HIV-HCV-Coinfection, and the Hepatocellular Carcinoma (HCC) Study Groups at the Medical University of Vienna, Austria. He is currently conducting a number a clinical trials in these indications and is running a translational lab testing novel approaches to the treatment of portal hypertension and HCC.

SS08-3

Art-Score to Select Patients for Retreatment of TACE

Markus Peck-Radosavljevic

Medical University of Vienna, Vienna, Austria

Transarterial chemoembolization (TACE) is the treatment of the choice for patients with intermediate stage liver cancer (BCLC-B) according to the EASL clinical practice guideline on the management of liver cancer as well as to several other international and national guidelines. TACE is in most cases only a palliative treatment and the problem with TACE is two-fold:

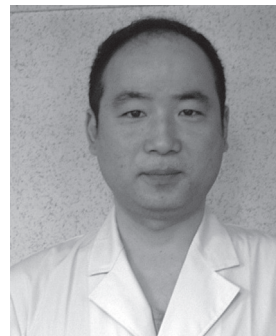
For one thing less than 40% of patients respond radiologically to TACE and only those derive a survival benefit from this treatment. On the other hand the occlusion of some of the arterial blood supplied to the liver does considerable damage to the liver function in some patients, so that the benefit of the antitumor treatment might be offset by a detrimental effect on liver function. For this reason, several groups have recently started to investigate the possibility to predict the outcome of patients undergoing TACE in liver cancer [1–3]. Validation of the Italian sub-classification gave a reasonably good survival difference between these different subgroups [4], a finding that was at least partially confirmed in a large Asian TACE cohort from Korea [5] but none of these scores was designed to predict tolerance to TACE. Our group in Vienna was interested in developing a score to predict fitness for retreatment with TACE after the first transarterial chemoembolization, considering that it would not be easy to predict at baseline either the radiologic response or the response of the cirrhotic liver to the ischemic insult incurred by TACE. We are able to develop and validate the ART-score [6], which by evaluation of changes in Child- Pugh status, tumor response, and AST-levels was able to reliably predict good and bad outcome after first TACE. Furthermore, the sequential application of the ART-score after each TACE cycle was able to select patients for retreatment with TACE reliably over time [7]. While prospective validation of any of these scores has not happen so far, the question of how to proceed with patients unfit for further TACE's has not been resolve so far and needs prospective evaluation in clinical trials.

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Speaker's Curriculum Vitae

Name Koichiro Yamakado, MD
Institution Department of Interventional
Radiology, Mie University



Dr. Yamakado graduated from Kanazawa University in 1987. He is now a chief of Department of Interventional Radiology in Mie University. He is a member of various national and international societies, including Japan Radiological Society, the Japanese Society of Interventional Radiology (JSIR), and RSNA.

SS08-6**Case Presentations from Japan***Koichiro Yamakado, MD*

Department of Interventional Radiology, Mie University, Japan

There is still a controversial for definition of TACE refractory HCCs. In this case presentation, we would like to show two cases who had TACE refractory HCCs according to guideline in Japan.

Speaker's Curriculum Vitae

Name Shigeki Arii, MD, PhD
Institution President of Hamamatsu Rosai Hospital, Japan Labour Health and Welfare Organization



1973 graduated from Kyoto University School of Medicine
1982 Assistant Professor of 1st Department of Surgery, Kyoto University School of Medicine
1994 Senior assistant Professor of 1st Department of Surgery, Kyoto University School of Medicine
1998 Associate Professor of 1st Department of Surgery, Kyoto University School of Medicine
2000 Professor and Chairman of Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University
2012 President of Hamamatsu Rosai Hospital, Japan Labour Health and Welfare Organization,
Professor emeritus of Tokyo Medical and Dental University

SS09-1

Surgical Treatment for Vascular Invasion of HCC

Shigeki Aii

Department of Hepatobiliary-Pancreatic Surgery, Tokyo Medical and Dental University; Hamamatsu Rosai Hospital (Japan Labour Health and Welfare Organization), Japan

Vascular invasion is well known to be a most significant prognostic variable in HCC.

According to the BCLC staging, portal invasion is not indicated to the surgery. Actually, the Japanese Guideline also recommends the treatment with Sorafenib to the cases with involvement to the portal trunk (Vp4) or first branch (Vp3). On the other hand, the patients with the smaller vessel invasion (Vp2, Vp1) are indicated to TACE or surgery. According to the Sharp study, MST of the patients with macroscopical portal involvement was 4.9 M in the Placebo group, and 8.1 M in Sorafenib group. The MST even in the sorafenib group, however, has not been satisfactory. According to the nationwide survey of the Liver Cancer Study Group of Japan, 5- year survival in Vpo, Vp1, Vp2, and Vp3 and 4 were 59.0% (n = 20195), 39.1% (1978), 23.3% (820), and 18.3% (1021), respectively.

In my experience at Tokyo Medical and Dental University, those were 80.5% (n = 288), 62.1% (150), 47.5% (50), and 16.3% (26), respectively. Approximately 60% of VP3–4 cases died of cancer recurrence within 1 year. MST is 303 days, while the long survivor more than 5 year is actually existed. The prognostic factor among the clinicopathological variables is found to be postsurgical intra-arterial chemotherapy by multivariate analysis. Then, the important strategy is to clarify the patients who will be provided with survival benefit by surgery, and to establish the optimal combination of surgery and chemotherapy. In this line of context, I will present surgical treatment for advanced HCC with vascular invasion.

Speaker's Curriculum Vitae

Name Jinsil Seong, MD, PhD
Institution Professor,
Department of Radiation Oncology,
Yonsei University College of
Medicine



Professor Jinsil Seong currently works at Department of Radiation Oncology, Yonsei University College of Medicine, Seoul. Prior to her current position, she has been a Visiting Scientist in Department of Experimental Radiotherapy, MD Anderson Cancer Center, Houston, USA. She graduated from Yonsei University College of Medicine, Seoul and subsequently completed her PhD degree from Yonsei University, Seoul.

Professor Seong is a former President of Yonsei Liver Cancer Study Group and also a member of various national and international societies including International Liver Cancer Association, Korean Liver Cancer Study Group, European Society for Therapeutic Radiology and Oncology and American Society for Therapeutic Radiology and Oncology. She served as a member of the Editorial Board of International Journal of Radiation Oncology Biology Physics for the past 10 years. Currently she is a council member of Asian Clinical Oncology Society as well as Asia Pacific Primary Liver Cancer Expert Meeting. She is also working as a consultant in International Atomic Energy Agency. She has been awarded many times for her credit including Korean Cancer Association Distinguished Scientific Award (2012), Best Presentation Award (bronze) in 2nd Asia Pacific Primary Liver Cancer Expert Meeting (2011) and Young Investigator Award in International Congress of Liver Disease (2004). She has published 93 articles in non-SCI listed journals and 100 articles in SCI listed journals. She has also delivered 106 talks at major national and international congresses. Research interest is "Radiotherapy of HCC" in clinical approach as well as in translational research.

SS09-2

Radiotherapy for Advanced but Liver-Confined Hepatocellular Carcinoma

Jinsil Seong

Radiation Oncology, Yonsei University Medical College, Korea

Advanced but liver-confined hepatocellular carcinoma (HCC) remains as a major therapeutic challenge. In this stage of locally advanced HCC (LAHCC), it frequently presents either huge mass infiltrating almost entire hemilobe of liver, multiple nodules, major vascular invasion, or combination of two or more of these entities. It also has a high potential of intra- or extra-hepatic metastasis. In oncologic principle, locally advanced diseases are managed in multimodality therapeutic approach; combination treatment of chemotherapy and radiotherapy maximizes local tumor control as well as suppression of cancer metastasis. In selected cases, combination treatment induces a substantial tumor regression and or downstaging so that surgical resection can be performed with curative intent.

In HCC, multimodal therapeutic approach has long been out of interest. Neither radiotherapy nor chemotherapy was far from satisfaction in their therapeutic efficacy. However, with revolutionary development of contemporary radiotherapy technology, delivery of tumoricidal dose of radiation can be possible with no lethal toxicity. While radiotherapy is mostly aiming at local tumor control, hepatic arterial chemotherapy can interact with radiotherapy to maximize therapeutic effect and suppression of mostly intrahepatic metastasis.

In our institute, combination of local radiotherapy and concurrent hepatic arterial chemotherapy (concurrent chemoradiotherapy; CCRT) has been set up and practiced since the first pilot study was successful. More than 800 LAHCC patients have been treated with CCRT. In a recent study comparing our series and national cohort of Korean Liver Cancer Study Group, propensity score analysis revealed significantly higher overall survival in CCRT group (11.4 vs. 6 months, $p = 0.01$). In selected patients (16.9%), CCRT induced a substantial tumor regression and compensating hypertrophy of non-tumor liver, which led to curative resection.

While CCRT for LAHCC has been successful in our institute, lack of evidence through randomized controlled trial remains as a problem to overcome. While efforts should be continued to build a solid evidence, the patients presenting LAHCC needs full consideration not only for improved survival but also for a narrow but a decent chance for cure.

Speaker's Curriculum Vitae

Name Shuntaro Obi, MD, PhD
Institution Director, Kyoundo Hospital, Tokyo, Japan;
Division Chief, Department of Gastroenterology and Hepatology, Kyoundo Hospital, Tokyo, Japan



Education/Post Graduate Training

College/University:

1985–1991 MD, Teikyo University School of Medicine

May 2007 PhD Gastroenterology Tokyo University School of Medicine #16800

Residency:

1991–1992 Resident in Internal Medicine, Surgery and Anesthesiology, Tama-Hokubu Medical Center, Tokyo, Japan

Resident in Obstetrics, Gynecology and Pediatrics, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

1992–1993 Resident in Internal Medicine, Tokyo University School of Medicine, Tokyo, Japan

Fellowship:

1993–1995 Fellow in Gastroenterology, General Hospital National Health Insurance Asahi Central Hospital, Chiba, Japan

Present Position or Academic Rank

2006–present Director, Kyoundo Hospital, Tokyo, Japan

2002–present Division Chief, Division of Gastroenterology and Hepatology, Kyoundo Hospital

2005–present Director, Sasaki Foundation

2008–present Assistant Professor in Gastroenterology, Tokyo University School of Medicine

2009–present Assistant Professor in Gastroenterology Teikyo University School of Medicine

2011–present Assistant Professor in Gastroenterology Kagawa University School of Medicine

2012–present Assistant Professor in Gastroenterology Yamanashi University School of Medicine

Previous Professional Positions and Appointments

1995–1998 Staff Physician, Internal Medicine (II), Tokyo University School of Medicine, Tokyo, Japan

1998–2002 Staff Physician, Gastroenterology, Tokyo University School of Medicine

Honors and Awards

2009 Fellowship Award from the Foundation for Promotion of Cancer Research

Fellowships

1999 Fellow of the Japanese Society of Gastroenterology

2005 Fellow of the Japanese Society of Internal Medicine

2010 Fellow of the Japanese Board of Cancer Therapy

SS09-3

Hepatic Arterial Infusion Chemotherapy Substantially Improved the Survival Rate Among the Responders

Shuntaro Obi, Sinpei Sato, Toshihiro Kawai, Takafumi Sugimoto, Yoko Yashima, Miho Kanda

Gastroenterology and Hepatology, Kyoundo Hospital of Sasaki Institute, Japan

Liver cancer is the sixth most common cancer worldwide in terms of numbers of cases but because of the very poor prognosis, the number of deaths is almost the same. It is therefore the third most common cause of death from cancer. The majority of these tumors develop in patients who have liver cirrhosis. The development of HCC has an effect in the natural history of liver disease. In spite of screening system, some HCCs are detected at an advanced stage. An increasing variety of therapeutic options are available for patients with HCC. Many of these options have survival benefit. However, their long term prognosis remains disappointing, because recurrence of HCC is encountered frequently, and portal venous invasion of HCC develops. According to the treatment algorithm of HCC, patients with advanced disease are candidates for Sorafenib. However it is proven to be effective by RCT, the result has limitation with severe adverse events. Several other therapies have been evaluated, including hepatic arterial infusion. However, there is no RCT evidence that those therapies could contribute to prolongation of survival, although marginal effects such as shrinkage of tumor size or decrease of tumor number have been observed in selected cases. Several randomized controlled trials have been planned to evaluate HAIC using Sorafenib as a control. These trials will clarify some of the uncertainties of HAIC.

Speaker's Curriculum Vitae

Name Pierce K.H. Chow, MBBS, M.Med (Surg), FRCSE, FAMS, PhD

Institution Senior Consultant Surgeon, Department of General Surgery, Singapore General Hospital; Visiting Consultant, National Cancer Centre; Professor, DUKE-NUS Graduate Medical School



Professor Pierce Chow is an academic surgeon and Professor at the Duke-NUS Graduate Medical School. He is concurrently Senior Consultant Surgeon at the National Cancer Centre Singapore (NCCS) and the Singapore General Hospital (SGH), and NMRC Senior Clinician Scientist. Professor Chow's interests are in oncology and the development of medical devices. He has successfully lead multi-disciplinary teams in translational oncology research and has been protocol chair of multi-national investigator-initiated clinical trials. He was conferred the 2012 NMRC National Outstanding Clinician Scientist Award for his research on Liver Cancer.

Professor Chow was the Chapter of Surgeon's Gold Medalist at the conjoint Royal College of Surgeons of Edinburgh/M.Med (Surgery) examination in 1994 and completed a clinical fellowship in Liver Transplantation in Australia in 2000. In 1995, he won the prestigious Young Surgeon's Award of the Academy of Medicine for his research into the patho-physiology of liver blood flow and regeneration. He has gone on to receive many other academic and professional awards. He has received 2 NMRC Research Fellowships (in 1995 and 1997) and in 2004 was conferred his PhD.

Professor Chow has published extensively on hepato-biliary cancers and gastrointestinal stromal tumours and carried out both preclinical and clinical research on brachytherapy in HCC and pancreatic cancers. He has more than 180 scientific papers, books and book chapters and advises both government and industry on biomedical research. He also has established a strong track record in experimental oncology and in clinical trials. He co-founded the Asia-Pacific Hepatocellular Carcinoma Trials Group in 1997 and has been the protocol chair of 5 multi-national trials. Currently, Professor Chow is the protocol chair of a 26-center investigator-initiated phase III trial that compares a selective internal radiation device (SIRsphere®) against molecular targeted therapy (sorafenib) in locally advanced HCC. The trial is funded jointly by both NMRC and industry and is conducted under the auspices of the Asia-Pacific Hepatocellular Carcinoma (AHCC) trials group. In 2012 he was conferred the National Outstanding Clinician-Scientist Award for his research on hepatocellular carcinoma.

SS09-4

Intra-Arterial Radiotherapy for Advanced HCC with Vascular Invasion

Pierce K.H. Chow

Duke-NUS Graduate Medical School, Singapore; National Cancer Center Singapore; Singapore General Hospital, Singapore

Vascular invasion including invasion thrombosis/invasion of the portal veins (PVT) and hepatic veins (HVT) is one of the most devastating features of Hepatocellular Carcinoma (HCC). PVT and HVT are harbingers of grave prognosis and are rapidly fatally. If not successfully treated, the survival of these patients is grave and among Hep B patients in the Asia-Pacific, has a median survival of between 3- 6 months. The only therapy proven to have some efficacy in these patients is currently sorafenib.

Existing data from retrospective as well as prospective phase II studies from our group and elsewhere have demonstrated that intra-arterial radiation therapy with yttrium-90 is efficacious in HCC with vascular invasion. Randomized controlled trials that investigates this efficacy rigorously in both the Asia-Pacific as well as in Europe are currently ongoing and will define the role of intra-arterial therapy in these patients. The implications of these are discussed.

Speaker's Curriculum Vitae

Name Josep M. Llovet, MD
Institution Professor of Research, ICREA, BCLC Group, Liver Unit, Hospital Clínic Barcelona; Professor of Medicine, Director, Division of Liver Diseases, Mount Sinai School of Medicine, New York



Josep M. Llovet is **Professor of Research-ICREA** in the BCLC Group, Liver Unit, IDIBAPS-Hospital Clínic of Barcelona (Spain), **Director of the HCC Program and Professor of Medicine** at the Mount Sinai School of Medicine, New York University (USA). Professor Llovet obtained his degree in Medicine and Surgery from the University of Barcelona in 1986 and his PhD from the Autonomous University of Barcelona in 1995.

Professor Llovet is **President of the International Liver Cancer Association (ILCA)** and Chairman of the European Clinical Practice Guidelines of management of liver cancer (EASL-EORTC). He has published more than 180 articles in peer-reviewed journals such as *New England Journal of Medicine*, *Nature Genetics*, *Lancet*, *Cancer Cell*, *Journal Clinical Investigation*, *Journal of Clinical Oncology*, *Lancet Oncology*, *Gastroenterology* and *Hepatology* (total citations 22,490, total impact factor 1876; h index 67), more than 40 chapters of books, and has delivered more than 400 lectures. He is Senior Editor of *Clinical Cancer Research* and Special Editor of *Gastroenterology* and *Journal of Hepatology*.

During the last 15 years, Dr. Llovet received the AACR-Landon International Award (2009), the International Hans Popper award (2012), Premi Josep Trueta (2013) and is leading international projects with competitive funding from the European Commission (FP7- HEALTH, HEPROMIC, 2010) and the US National Institute of Health (R01, 2008). Below, find described the scientific and managerial positions and the main scientific achievements obtained. He has contributed to advancing knowledge in the following areas:

1. Clinical classification of HCC: With the acronym BCLC (Barcelona-Clínic Liver Cancer) classification, first published in Llovet, *Semin Liv Dis* 1999, and then further modified in Llovet, *Lancet* 2003; Llovet, *J Natl Can Inst*, 2008 and Forner, *Lancet* 2012. This classification has been adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.

2. Establishment of chemoembolization as standard of care: In patients with intermediate HCC. Evidence-based establishment through randomized controlled trials [Llovet, *Lancet* 2002] and meta-analysis [Llovet, *Hepatology* 2003] of chemoembolization as standard of care in patients with intermediate HCC. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.

3. Establishment of sorafenib as standard of care: In patients with advanced HCC (Llovet, *New Engl J Med* 2008). This breakthrough achievement establishes sorafenib as first line treatment for advanced HCC, and represents the first identification of survival advantages with systemic treatments. Identified by *Nature Medicine* as the most cited paper in oncology 2008–2010. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.

4. Guidelines of management of HCC: Chair of EASL-EORTC Guidelines, 2012 (*J Hepatol*, 2012, *Eur J Cancer* 2012), and committee member of guidelines of EASL (2001). Leading author of AASLD guidelines for design of clinical trials in HCC (Llovet, *J Natl Cancer Institute*, 2008).

5. Establishment of a molecular diagnosis of HCC: Gene-set (3 genes) based diagnosis of HCC reported in Llovet, *Gastroenterology* 2006, and included in EASL-EORTC guidelines.

6. Proposal of a molecular classification of HCC and ICC: A final proposal of a molecular classification of HCC is based on the results reported in different publications (Wurmbach, *Hepatology* 2007; Hoshida, *New Engl J Med*, 2008, Chiang, *Cancer Res*, 2008; Hoshida, *Cancer Res* 2009, Villanueva, *Gastroenterology* 2011; Sia, *Gastro* 2013, Hoshida, *Gastroenterology* 2013).

7. Identification of drivers of oncogenesis as targets for therapies: Several studies led to the identification of **Akt/mTOR pathway** [Villanueva *Gastroenterology*, 2008], **Ras pathway** [Newell, *J Hepatol* 2009], **EGFR pathway** [Keng, *Nature Biotech* 2009], **IGF pathway** [Tovar, *J Hepatol*, 2011], **Wnt Pathway** [Lachenmeyer, *CCR* 2012], **Notch pathway** [Villanueva, *Gastroenterology* 2012], **AEG** [Yoo, *J Clin Invest* 2009] and **miRNAs** [Viswanathan, *Nat Genetics* 2009, Toffanin, *Gastroenterology* 2011] as drivers of hepatocarcinogenesis and potential targets for therapies.

SS09-5**Systemic Therapy in HCC: Sorafenib***Josep M. Llovet*

ICREA, BCLC Group, Liver Unit, Hospital Clínic Barcelona, Spain; Division of Liver Diseases, Mount Sinai School of Medicine, New York, USA

Hepatocellular carcinoma (HCC) has increased its mortality in the US and Europe in the last decades. Since most patients are still diagnosed at advanced stages, there is an urgent clinical need for developing novel systemic agents. In this setting, sorafenib, a tyrosine kinase inhibitor (TKI) with blockade activity against BRAF, VEGFR and PDGFR, has demonstrated its antitumor activity by significantly improving survival of patients with advanced HCC. The phase III clinical trial (SHARP) was conducted in 602 patients with advanced HCC. The study was stopped at the interim analysis because of survival advantages favoring sorafenib (n = 299) vs placebo (n = 303). Based on 321 deaths, the hazard ratio sorafenib/placebo was 0.69 (95% CI: 0.55, 0.86; p = 0.0005), representing a 31% decrease in the risk of death with a median survival for sorafenib arm of 10.6 months vs 7.9 months for placebo. In addition, sorafenib showed a significant benefit in terms of time to progression (TTP) assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo. Grade 3/4 adverse events such as diarrhea (sorafenib vs placebo: 11% vs 2%) and hand-foot skin reaction (8% vs 1%) were more frequent with sorafenib. Drug discontinuation due to sorafenib adverse events was of 15%, but drug-related adverse events were considered manageable and no death related with toxicity was described. Subgroup analysis showed that patients with HCV-related HCC obtained a very remarkable benefit from sorafenib therapy. The beneficial effect of sorafenib was confirmed in HBV-related HCC in the Asian Pacific trial, where overall survival favored sorafenib compared to placebo with a HR:0.69. Companion biomarker studies exploring subpopulations of HCC patients responding to sorafenib were unable to identify those subgroups of patients, despite the fact that high c-Kit and low HGF plasma levels were associated with a trend of better survival.

The consequences of the trial are three-fold. First, sorafenib has become the standard of care for patients with advanced HCC and also for those progressing after loco-regional therapies. This statement has been endorsed by the EASL-EORTC and AASLD guidelines, and has modified the accepted treatment schedule. Hence, sorafenib is established as the control arm for future trial design in this setting. Second, the study proves that targeted therapies are active in this otherwise chemo-resistant tumor. Thus, this opens an avenue for combination therapies blocking different pathways. Finally, few studies are currently exploring the potential subgroup of patients that benefit most from sorafenib therapy.

Speaker's Curriculum Vitae

Name Kazuto Nishio, MD, PhD
Institution Professor and Chairman,
Department of Genome Biology,
Kinki University Faculty of
Medicine



Professional History:

1986 Graduate of Wakayama Medical University, MD Degree
1988–1990 Medical Staff, Fourth Department of Internal Medicine, Wakayama Medical University Hospital
1990–1992 Research Resident, Foundation for Promotion of Cancer Research at National Cancer Center Research Institute
1992–1996 Research Staff, Pharmacology Division, National Cancer Center Research Institute
1994 PhD Degree, Wakayama Medical University
1996–2006 Head, Section of Drug Resistance, National Cancer Center Research Institute
2000–2006 Director, Translational Research Laboratory, National Cancer Center Hospital
2003–present Invited Professor, Department of Internal Medicine, Kitasato University School of Medicine
2005–present Expert Member, Pharmaceuticals and Medical Devices Agency
2006–present Professor and Chairman, Department of Genome Biology, Kinki University School of Medicine
2006–2007 Invited Researcher, Genetics Division, National Cancer Center Research Institute
2010–present Invited Professor, Kyoto Prefectural Medical University

Research Interests:

Translational Research (Molecular Correlative Study), Anticancer Drugs, Signal Transduction, Drug Resistance, Molecular Targeted Agents

Membership of Academic Societies:

Japanese Cancer Association (Councilor), Japanese Society of Medical Oncology (Director), Japanese Association for Molecular Target Therapy of Cancer (Director), Japan Society of Clinical Oncology (Councilor), Japanese Society of Chemotherapy (Councilor), Japan Lung Cancer Society (Scientific Committee Member), American Association for Cancer Research, American Society of Clinical Oncology, International Association for the Study of Lung Cancer and others.

SS10-2

Predictive Biomarker of Molecular Targeted Agents and Precision Medicine for HCC

Kazuto Nishio, Kazuko Sakai, Yasuo Kodera

Department of Genome Biology, Kinki University Faculty of Medicine,
Japan

Developments of various molecular targeted agents are in progress for HCC patients. One of those agents is now available for HCC patients. Additionally, development of predictive biomarkers of molecular targeted agents is an important issue for the precision medicine. Sorafenib is a multi-kinase inhibitor and shows cytostatic action on the most of the patients, but some HCC patients (~1–3%) achieve hyperresponse to sorafenib.

We analyzed HCC tumor specimens of the sorafenib hyperresponders and demonstrated that the tumors with amplification of 11q-13 regions might show hyper-response to sorafenib. Our preclinical studies reveal that the cancer cells with 11q-13 amp are highly sensitive to FGFR inhibitors. Successive preclinical study revealed the FGF4 might be a driver for the HCC. These findings allow us to develop FGFR inhibitors for the tumors with 11q-13 amp or FGF4 amp as well as FGFR mutations and these amplifications as markers for companion diagnosis.

On the other hand, a small part of the tumors without 11q-13 amp also exerts hyperresponse to sorafenib. We are profiling the molecular characteristics of hyperresponded tumors. Targeted deep-sequencing detected the gene amplification and kinase domain mutations of target and off-target genes in the tumors of hyper-responders. The association of the gene alterations with sensitivity to sorafenib is under investigation. In other cases, the somatic mutation of an adaptor gene was detected by deep-sequencing. We will re-analyze the whole exons of the adaptor genes comprehensively.

For precision medicine with molecular targeted agents, companion diagnosis using multiplex technology is essential. Liquid biopsy as well as deep sequencing will be powerful tool for this strategy. We have developed a multi-gene panel (digital PCR-NGS hybrid system) for liquid biopsy. This technology allows us to monitor the treatment effect of patients with re-biopsy. In near future we should discuss how to conquer acquired resistance to molecular targeted therapy in HCC as well as RCC and lung cancer. To elucidate the mechanisms of the acquired resistance is important issue for the development of the next generation therapeutics.

Speaker's Curriculum Vitae

Name Peter Robert Galle, MD, PhD
Institution University Medical Center Mainz
Position Direktor 1st Medical Department



Dr. Galle majored in internal medicine at the Universities of Berlin and Marburg/Germany, Hammersmith Hospital, London/UK and University of Texas/USA and received his MD degree from Marburg University and PhD degree from Heidelberg University.

Initially he held a position as postdoctoral fellow in Molecular Biology at the Centre for Molecular Biology Heidelberg working on the replication of hepatitis B viruses. Afterwards he completed his residency in Internal Medicine and Gastroenterology at the University Hospital of Heidelberg. In 1998 he became Director of the I. Medical Department in Mainz and from 2005–2008 he held the CEO position of Mainz University Hospital.

He is member of several national and international societies such as the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), and serves as Co-editor for the Journal of Hepatology and is on the Editorial Boards of several other Journals. He is member of the Executive Board and President of the International Liver Cancer Association (ILCA).

His research has focused on elucidating important aspects of apoptotic cell death in the liver, immune escape of tumour cells, and preclinical and clinical research in HCC. He was awarded several prizes, amongst others the prestigious Tannhauser award, the highest prize of the German Society for Digestive Diseases. He has published more than 350 peer-reviewed papers.

Google Scholar Citation Report (17.03.2014)

Sum of the Times Cited: 31,144

h-index: 82

SS11-1

Signal Transduction and New Molecular Targets in Hepatocellular Carcinoma

Peter R. Galle

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The molecular processes that drive the transformation of normal hepatocytes into malignant cells, such as those occurring during the development of hepatocellular carcinoma (HCC), are complex. Two early pathogenetic steps have been identified. Firstly, in most cases, liver cirrhosis presents with a precancerous lesion following viral hepatitis infection, excessive alcohol consumption or exposure to environmental toxins. Secondly, mutations occurring in one or more genes accumulate, either in the context of chronic inflammation or as the result of direct DNA damage. This results in aberrations in several cellular signalling pathways that are important for tumour angiogenesis and the survival and proliferation of tumour cells.

The knowledge of signalling pathways controlling proliferation and angiogenesis has – after years of therapeutic nihilism – resulted in the development of the multikinase inhibitor sorafenib as the first agent to demonstrate a significant improvement in the survival of patients with advanced hepatocellular carcinoma (HCC). However, survival benefits on sorafenib treatment remain modest in clinical practice and further clinical trials on other targeted agent so far failed to demonstrate a relevant clinical benefit in phase III trials in first- or second-line settings. In addition, according to a recent press release sorafenib failed in the adjuvant setting.

One explanation for this detension in the development of therapeutical strategies in HCC ist the general lack of available tumor tissue which would help to identify subgroups of patients benefitting from novel strategies. This is in contrast to other tumors such as lung cancer where molecular subgrouping is already reality.

Given the current problems in successfully treating HCC, we need to aim for novel therapeutic strategies. Besides the characterization of predictive signatures to subgroup patients with HCC, understanding and unravelling the characteristics of stem cell biology in HCC may pave the road to such novel strategies.

The presentations will discuss signal transduction and new molecular targets in HCC.

Speaker's Curriculum Vitae

Name Andrew X. Zhu, MD, PhD
Institution Massachusetts General Hospital
Cancer Center; Harvard Medical
School



Dr. Andrew X. Zhu is Director of Liver Cancer Research at Massachusetts General Hospital Cancer Center and an Associate Professor of Medicine at Harvard Medical School. The major focus of his research is to develop more effective therapies for hepatocellular carcinoma (HCC) and biliary tract cancers (BTCs) through phase I, II and III clinical trials. The second area of his research interests is highly complementary and is directed at the development of novel circulating and imaging biomarkers for targeted therapeutics that have prognostic and/or predictive significance. The third area of his research is to define and characterize known or novel genetic mutations in HCC and BTCs and assess their potential correlation with clinical outcomes and as therapeutic targets.

As a widely published author, Dr. Zhu has served as a principle investigator in many clinical trials in HCC, BTCs and other gastrointestinal cancers. He is the invited reviewer for many medical journals and has lectured extensively on HCC and other gastrointestinal cancers. An internationally recognized leader in HCC, he has led early efforts of developing several molecularly targeted agents in HCC and studying the predictive and surrogate circulating and imaging biomarkers. He is a founding board member of the International Liver Cancer Association, Fellow of American College of Physicians, and a member of the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research. Dr. Zhu serves on the Hepatobiliary Cancer committee of the National Comprehensive Cancer Network, the Grants Selection Committee of ASCO, and the Hepatobiliary Cancer Task Force of The NCI Gastrointestinal Cancer Steering Committee (GISC).

SS11-2

Targeting mTOR Pathway in HCC: Lessons Learned from Everolimus Development

Andrew X. Zhu

Massachusetts General Hospital Cancer Center; Harvard Medical School, Boston, MA, USA

Worldwide, hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death. Advanced HCC carries a poor prognosis and systemic therapy with cytotoxic agents provides marginal benefit. Improved understanding of the mechanism of hepatocarcinogenesis coupled with the arrival of many newly developed molecularly targeted agents has provided the unique opportunity to study some of these novel agents in advanced HCC. Despite the successful approval and extensive application of sorafenib, the prognosis for patients with advanced HCC remains poor and the benefits with sorafenib are modest. Currently there are no established biomarkers for sorafenib mediated clinical benefits. Therefore there is an unmet need for developing other molecularly targeted agents in advanced HCC.

Mammalian Target of Rapamycin (mTOR) is a serine/threonine kinase that plays a critical role in regulating protein translation, cell cycle progression, and cellular function. Activation of mTOR signaling has been identified in approximately 50–60% of HCC. Recent studies using knockout mice showed that mTOR activation was sufficient to cause HCC, indicating the pivotal role of mTOR signaling in HCC. Allosteric mTOR inhibitor everolimus has been tested in a randomized, placebo-controlled phase III clinical trial in patients with advanced HCC who failed sorafenib (EVOLVE-1). Median overall survival, the primary endpoint, showed no improvement with everolimus treatment versus placebo, but a small subset of patients showed response. The molecular predictors for those who benefited from the everolimus treatment are currently being explored. Despite the failure of everolimus in a phase III trial, other mTOR inhibitors, such as temsirolimus and sirolimus, and a dual inhibitor of TORC1/TORC2 (CC-223) are under early clinical development in HCC.

Speaker's Curriculum Vitae

Name Richard S. Finn, MD
Institution Associate Professor of Medicine,
Division of Hematology/Oncology,
UCLA David Geffen School of
Medicine,
University of California, Los
Angeles



Dr. Finn is an Associate Professor of Medicine at the UCLA David Geffen School of Medicine where he is the lead oncologist in the Multi-Disciplinary Liver Cancer Clinic. He is also director of the Translational Research Laboratory in the division of Hematology/Oncology and co-director of the Signal Transduction Program in the Jonsson Comprehensive Cancer Center at UCLA.

He currently splits his time between patient care and laboratory and clinical research. His research interests lie in the development of molecular targeted agents and biomarkers in liver cancer and breast cancer. Dr. Finn has served as principal and sub-investigator in trials exploring the use of targeted therapies in breast and hepatocellular cancers. He has a particular interest in identifying predictive markers of response to novel therapeutics. His work has been published in journals such as *Journal of Clinical Oncology*, *Cancer Research*, *Clinical Cancer Research*, *Hepatology*, *Cancer Cell* and elsewhere; Dr. Finn has also given oral presentations at major meetings including American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO), and International Liver Cancer Association (ILCA) annual meetings.

Dr. Finn is a member of ASCO, American Association of Cancer Research (AACR). He is on the governing board of the International Liver Cancer Association (ILCA) and is a senior editor for *Hepatic Oncology* and is on the editorial board of *Clinical Cancer Research*.

SS11-3**Ongoing Trials***Richard S. Finn*Division of Hematology/Oncology, UCLA David Geffen School of
Medicine, University of California, Los Angeles, USA

As a leading cause of cancer related death world-wide, outcomes for patients with advanced HCC still remain poor. Since the approval of sorafenib in 2007 there has been a surge in clinical activity in all stages of HCC. More than ever there is a large number of novel therapeutics being studied for patients with advanced HCC as well as in combination with local therapies and in the post-operative/adjuvant setting. Unfortunately, despite a great investment there have not been any new agents approved in the management of HCC since sorafenib. This is complicated by the fact that we are still defining the natural history of HCC in the post-sorafenib era and validating endpoints in clinical trials. Currently, there are a number of Phase III studies in the front-line and second-line setting ongoing. We will review these studies in regard to their design and endpoints as well as the rationale behind them. We will also highlight some compounds in early development and offer insights on how to minimize the risk of failures in future trials.

Speaker's Curriculum Vitae

Name Etsuro Hatano, MD, PhD
Institution Associate Professor,
Division of Hepatobiliary
Pancreatic Surgery and
Transplantation,
Department of Surgery,
Graduate School of Medicine,
Kyoto University



Etsuro Hatano studied Medicine at Kyoto University and graduated in 1989. Following this, he completed a clinical fellowship in Kyoto University Hospital, Takayama Red Cross Hospital, and Wakayama Red Cross Hospital. He graduated from Graduate School of Medicine, Kyoto University in 1997, where he received his PhD degree in Medical Science, followed by a research fellowship at Graduate School of Medicine, Kyoto University and the University of North Carolina at Chapel Hill in the United States. Dr. Hatano is currently an associate professor at Department of Surgery, Graduate School of Medicine, Kyoto University.

Major Topics:

Multidisciplinary treatment including living related liver transplantation and hepatic resection for hepatobiliary malignancies; Less-invasive surgery; Extension of indication for liver surgery.

MW01-1

Diagnosis of Microvascular Invasion

Etsuro Hatano, Satoru Seo, Kojiro Taura, Kentaro Yasuchika, Shinji Uemoto

Department of Surgery, Graduate School of Medicine, Kyoto University, Japan

Microvascular invasion (MVI) is an important risk factor for early recurrence of hepatocellular carcinoma (HCC), but preoperative prediction of MVI is difficult. The incidence of MVI ranged to 12–50% in HCC specimens from the patients undergoing hepatic resection. Diagnostic imaging modalities still have limitations to detect MVI. However, recent reports showed diffusion-weighted MRI, Gd-EOB-DTPA-MRI, and contrast-enhanced ultrasonography, were useful for detecting MVI. Furthermore, several factors, such as tumor size, L3-AFP, and DCP, were associated with positive MVI. Recently, Shirabe et al. demonstrated tumor size, DCP, and SUV on FDG-PET were independent clinical predictors for MVI. The sensitivity and specificity of scoring system designed using these three variables were 100% and 90.9%, respectively. Among the MVI-positive patients, the disease-free survival rates were significantly better in patients with wide surgical margin (SM), compared with that in those with narrow SM. Therefore, it should be considered to select surgical resection as first line treatment in stead of RFA, when predicting MVI.

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Speaker's Curriculum Vitae

Name Shunichi Ariizumi, MD
Institution Department of Surgery,
Institute of Gastroenterology,
Tokyo Women's Medical University



Education:

4/1987–3/1993 School of Medicine, St. Marianna Univ.
10/2000 Degree of Medical Science (PhD), Tokyo Women's Medical Univ.

Post-Doctor Training:

4/1993–3/1998 Residency, Dept. of Surgery, Institute of Gastroenterology, Tokyo Women's Medical Univ.

Positions and Appointments:

1995–1999 Assistant Medical Staff, Dept. of Surgery, Institute of Gastroenterology, Tokyo Women's Medical Univ.
1999–2002 Medical Staff, Yokohama General Hospital (Yokohama, Japan)
2002–2012 Medical Staff, Dept of Surgery, Institute of Gastroenterology, Tokyo Women's Medical Univ.
2012–2013 Assistant Professor (Lecturer), Dept of Surgery, Institute of Gastroenterology Tokyo Women's Medical Univ.
2013–2014 Dept of General, Visceral and Cancer Surgery, University of Cologne, Germany
2014– Assistant Professor (Lecturer), Dept of Surgery, Institute of Gastroenterology, Tokyo Women's Medical Univ.

Memberships (Professional Societies):

Japanese Surgical Society
Japanese Hepato-Biliary Pancreatic Surgery Society
Japanese Society of Gastroenterological Surgery
Japanese Society of Gastroenterology
International Hepato Pancreato Biliary Association

Publications:

Original Articles: 43

Awards:

Encouraging prize for international communication, Japanese Society of Gastroenterological Surgery, 2008
Prize from an academic society, Japanese Hepato-Biliary Pancreatic Surgery Society, 2012

MW01-2**Repeat Hepatectomy for Patients with Intrahepatic Recurrence of Hepatocellular Carcinoma***Shunichi Ariizumi, Satoshi Katagiri, Yoshihito Kotera, Yutaka Takahashi, Hiroto Egawa, Masakazu Yamamoto*

Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Japan

Background: Intrahepatic recurrence of hepatocellular carcinoma (HCC) is particularly high, even when curative hepatic resection can be performed. Management and optimal treatments for recurrent HCC have not been clarified in detail.

Methods: Between 2000 to 2011, 761 patients with HCC underwent curative hepatectomy. After hepatectomy, HCC was recurred in 422 of 761 patients. For patients with intrahepatic recurrence, repeat hepatectomy (LH), radiofrequency ablation (RFA), and trans-arterial chemoembolization (TACE) were performed.

Results: The recurrence pattern was intra hepatic recurrence in 354 patients (84%), extra hepatic recurrence in 37 patients (9%), intra hepatic recurrence with tumor thrombus in 21 patients (5%), and intra-with extra hepatic recurrence in 10 patients (2%). The 5-year survival rate after treatment for recurrent HCC was 41% for intra hepatic recurrence, 29% for extra hepatic recurrence, and 0% for intra hepatic recurrence with tumor thrombus and for intra-with extra hepatic recurrence. In patients with single intrahepatic recurrence, the 5-year DFS and OS were significantly better in the LH group (34% and 57%) than in the RFA group (13% and 63%) and the TACE group (5% and 44%). In patients with multiple intrahepatic recurrences, the 5-year DFS and OS were significantly better in the LH group (6% and 39%) and the RFA group (0% and 38%) than in the TACE group (0% and 16%).

Conclusions: Repeat hepatectomy is optimal treatment for a single intrahepatic recurrence of HCC.

Speaker's Curriculum Vitae

Name Myron Eliot Schwartz, MD
Institution Mount Sinai School of Medicine



Academic Appointments:

7/02 Professor of Surgery, Mount Sinai School of Medicine, New York, N.Y.
12/93–6/02 Associate Professor of Surgery, Mount Sinai School of Medicine, New York, N.Y.
7/87–12/93 Assistant Professor of Surgery, Mount Sinai School of Medicine, New York, N.Y.
7/85–6/87 Instructor in Surgery, Mount Sinai School of Medicine, New York, N.Y.

Hospital Appointments:

7/12 Director of Liver Surgery, Recanati Miller Transplantation Institute
7/04 Director, Surgical Oncology, Associate Director, Liver Transplantation
7/02 Director, Adult Liver Transplantation and Hepatobiliary Surgery
1/99–6/02 Deputy Director, Liver Transplantation, Chief, Hepatobiliary Surgical Services
7/77–10/80 Director, Craigsville Medical Center, Craigsville, VA
7/87–6/89 Section Chief, Bronx Veterans Admin Hospital, Bronx, N.Y.
1/91–12/98 Associate Director, Division of Liver Transplantation
12/93 Associate Attending, Mount Sinai Hospital, New York, N.Y.
7/87–12/93 Assistant Attending, Mount Sinai Hospital, New York, N.Y.
1/78–10/80 Medical Examiner, Augusta County, VA
7/77–10/80 Attending Physician, Kings' Daughters' Hospital, Staunton, VA

Education:

1976 MD, Jefferson Medical College, Philadelphia, PA
1974 B.S. (Summa cum laude), Pennsylvania State University, State College, PA

Postdoctoral Training:

7/86–6/87 Fellow, Vascular Surgery, Mount Sinai Hospital, New York, N.Y.
7/85–6/86 Chief Resident, General Surgery, Mount Sinai Hospital, New York, N.Y.
7/81–6/85 Resident, General Surgery, Mount Sinai Hospital, New York, N.Y.
7/76–6/77 Rotating Internship, Mercy Catholic Medical Center, Darby, PA

Certification:

10/88 American Board of Surgery, Certified in General Vascular Surgery, ID# 100100
10/87 American Board of Surgery, Certified in General Surgery, ID# 32710

Licensure:

3/83 New York #146980
5/77 Virginia #29046

Honors and Awards:

1998 Physician of the Year Award, Transplant Recipients' International Organization
1986 Arthur Aufses Sr.; Prize in Surgery
1975 Alpha Omega Alpha; Medical Honor Society
2012 Doctorate Degree Honoris Causae; Favolaro University, Buenos Aires, Argentina

MW01-3

Treatment of Recurrent Hepatocellular Carcinoma

Myron E. Schwartz

Mount Sinai School of Medicine, New York, NY, USA

Recurrence After Resection: Recurrence of HCC is common after resection, occurring in up to 75% of patients within five years. The large majority of recurrences are in the liver. Early (within the first 2 years) recurrence is usually the result of previously-unrecognized metastasis, whereas later recurrence is typically the result of *de novo* tumor development. The approach to intrahepatic HCC recurrence is similar to that for the primary tumor: patients with single tumor, Child's A, and no portal hypertension are offered resection, Patients who are not resection candidates and who have HCC within Milan criteria are considered for transplant, and locoregional therapies are applied according to guidelines. Results of second resection are similar to those achieved with first resection.

Recurrence After Transplant: Recurrence after transplant is by definition metastatic disease, and carries a poorer prognosis than recurrence after resection. Independent predictors of survival among patients with recurrence after transplant include time to recurrence < 1 year, high grade HCC, and the presence of bone metastasis. There is a select group of patients with an isolated site of recurrence, most commonly in the liver or lung, for whom resection or other locoregional treatment can prolong survival. Systemic therapy with sorafenib, while not specifically tested in the posttransplant setting is widely employed. The role of transplant immunosuppression in the development and progression of recurrence remains a matter of conjecture, but most transplant programs either add or substitute an mTOR inhibitor (everolimus/sirolimus) when recurrence is noted.

Speaker's Curriculum Vitae

Name Satoru Imura
Institution Department of Surgery,
The University of Tokushima



1) Education

Degrees/Diplomas/Licensures and Certifications

1997 MD, Tokushima University, School of Medicine

2004 PhD, Tokushima University

2) Professional Training and Employment

a) Academic Appointment

2004–2013 Assistant Professor, Department of Surgery, Tokushima University, Tokushima, Japan

2014– Project Professor, Department of Minimum Invasive and Tele-surgery, Tokushima University Hospital, Tokushima, Japan

b) Previous Appointments

1997–1998 Resident, Department of Surgery, Tokushima University Hospital, Tokushima, Japan

1998–1999 Medical Staff, Department of Surgery, Takamatsu Municipal Hospital, Takamatsu, Japan

1999–2000 Medical Staff, Department of Surgery, Shikoku Chuo Hospital, Shikoku chuo, Japan

2000–2001 Medical Staff, Department of Surgery, Anan Kyohei Hospital, Anan, Japan

2001–2004 Fellow, Department of Surgery, Tokushima University Hospital, Tokushima, Japan

c) Clinical Experience

Discipline: General Surgery

Specialty: Liver Surgery

3) Professional Affiliations and Activities

Japan Surgical Society

The Japanese Society of Gastroenterological Surgery

The Japan Society of Hepatology

The Japanese Association of Hepato-Biliary-Pancreatic Surgery

The Japanese Society of Gastroenterology

Japan Society for Endoscopic Surgery

The Japan Society of Clinical Oncology

Japanese Cancer Association

The Japan Society for Transplantation

American College of Surgeons

European Society for Organ Transplantation

International Association of Surgeons, Gastroenterologists and Oncologists etc.

MW01-4**Post-Hepatectomy Adjuvant Therapy for HCC with Macroscopic Portal Vein Invasion**

Satoru Imura, Mitsuo Shimada, Yusuke Arakawa, Yuji Morine,
Toru Utsunomiya

Department of Surgery, The University of Tokushima, Japan

Background/Aims: Recently, we have reported the anti-tumor effects of pegylated IFN α 2b (Peg-IFN α) on invasion, proliferation, neovascularization, *in vitro* and *vivo* (J Surg Res 2012). We herein introduce the effect of our new systemic adjuvant therapy consisting of IFN-alpha (IFN), 5FU and cisplatin (CDDP) after hepatectomy on advanced HCC with macroscopic portal invasion.

Methods: Thirty-one patients who had HCC with Vp2 or more of macroscopic portal invasion were included. Those patients were retrospectively divided into two groups: control group (n = 16), in which no adjuvant therapy was performed; and IFP group (n = 15), in which one cycle of subcutaneous injection of IFN (5MIU, 3 times/week, 4 weeks) and systemic intravenous administration of 5FU (500 mg/day, 5 days/week, 4 weeks) and CDDP (5 mg/day, 5 days/week, 4 weeks) was done as soon as possible within one month after surgery. Clinicopathological variables were compared between the two groups, including patient survival and disease-free survival (DFS).

Results: The overall survival rate in IFP group was higher than in control group (1 year: 100% vs. 37%, 3 year: 62% vs. 25%). Regarding the DFS, the DFS in IFP group was also significantly better than that in control group (1 year: 33% vs. 25%, 3 year: 33% vs. 19%). Regarding the recurrent patterns, a clear difference was observed between the two groups. In the IFP group, six of nine patients had controllable recurrent tumors (≤ 3 nodules) in the remnant liver, although 12 of 13 patients with recurrence had either distant metastasis or multiple (> 3 nodules) recurrent tumors in the remnant liver in the control group. Interestingly, in subclass analysis of HCC with Vp3 or more of portal invasion, drastic differences were observed both in patient survival and in disease-free survival between IFP and control groups.

Conclusions: Our new adjuvant regimen of systemic INF+5FU+CDDP may be a promising strategy after radical resection for HCC with macroscopic portal invasion.

Speaker's Curriculum Vitae

Name Toshimi Kaido, MD, PhD
Institution Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Graduate School of Medicine, Kyoto University



Education:

1987 Graduated from Kyoto University
1996 Graduated from Graduate School of Medicine, Kyoto University

Career:

1998–1999 Research associate, Institute for Frontier Medical Sciences, Kyoto University
1999–2001 Assistant Professor, First Department of Surgery, Kyoto University
2001–2007 Department of Surgery, Otsu Municipal Hospital
2007–2009 Assistant Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Kyoto University
2009, Oct- Associate Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Kyoto University

Awards (recent only):

2007 President award of the 19th Meeting of Japanese Society of Hepato-Biliary-Pancreatic Surgery
2008 Chairman award of the 20th Meeting of Japanese Society of Hepato-Biliary-Pancreatic Surgery
Best subject award of the 21th Annual Meeting of Japan Society for Surgical Infection
Excellent poster award of Japan Digestive Disease Week 2008
2009 Best subject award of the 45th Annual Meeting of the Japanese Society of Hepatology
2012 Fellowship award of Japanese Society for Parenteral and Enteral Nutrition (JSPEN) 2012
2013 Best subject award of the 15th AJINOMOTO Award in the 49th Annual Meeting of the Japanese Society of Hepatology
Best Paper in the Year of JSPEN
2014 IHPBA 2014 Best Oral Award

MW02-2

Usefulness of Kyoto Criteria as Expanded Selection Criteria for Liver Transplantation for Hepatocellular Carcinoma

Toshimi Kaido, Kohei Ogawa, Akira Mori, Etsuro Hatano, Shinji Uemoto

Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Graduate School of Medicine, Kyoto University, Japan

Background: We proposed expanded selection criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC), the Kyoto criteria, involving a combination of tumor number ≤ 10 , maximal diameter of each tumor ≤ 5 cm, and serum des-gamma-carboxy prothrombin levels ≤ 400 mAU/mL, and we have used these criteria since January 2007. In the present study, the usefulness of the criteria was prospectively as well as retrospectively validated.

Methods: Two hundred and eleven patients with HCC who underwent living donor LT (LDLT) at our institute between February 1999 and December 2013 were enrolled in this study. Overall survival and the recurrence rate were investigated in patients classified according to the Kyoto criteria and the Milan criteria. Tumor biological aggressiveness, including microvascular invasion and histological differentiation, according to the criteria was also examined.

Results: The 5-year overall survival rate for patients within the Kyoto criteria (83%) was significantly higher than that for patients exceeding them (48%) ($P < 0.001$). The 5-year recurrence rate for patients within the Kyoto criteria (5%) was significantly lower than that for patients exceeding them (49%) ($P < 0.001$). The 5-year overall survival rate did not differ significantly between patients in the Milan-in/Kyoto-in group ($n = 42$, 82%) and those in the Milan-out/Kyoto-in group ($n = 112$, 88%) ($P = 0.279$). Intention-to-treat analysis of the 74 patients who underwent LDLT after implementation of the Kyoto criteria showed that the 5-year overall survival rate and the recurrence rate were 80% and 7%, respectively. The incidence of microvascular invasion and poorly differentiated HCC were significantly lower in patients within the Kyoto criteria (22% and 16%) than in patients exceeding the Kyoto criteria (63% and 33%) ($P < 0.001$ and $P = 0.010$, respectively).

Conclusions: The Kyoto criteria incorporating biological marker are simple and useful expanded criteria for LDLT for HCC and could help achieve favorable outcomes.

Speaker's Curriculum Vitae

Name Yasuhiko Sugawara
Institution Department of Surgery, University of Tokyo



Position Title:
Associate Professor

Education/Training:

1990: Graduate Faculty of Medicine, University of Tokyo, Tokyo, Japan cum laude, MD
1995–1997: Graduate School of Medicine, University of Tokyo, Tokyo, Japan PhD
1997–1998: Liver Transplantation Surgery, Department of Hepatobiliary Pancreatic Surgery, National Cancer Center, Tokyo, Japan, Chief Resident
1999–2001: Artificial Organ & Transplantation Surgery, University of Tokyo, Tokyo, Japan, Instructor
2001–present: Artificial Organ & Transplantation Surgery, University of Tokyo, Tokyo, Japan, Associate Professor

Liver Transplantation – Editorial Board
Transplantation – Editorial Board

MW02-3

Liver Transplantation for Hepatocellular Carcinoma

*Yasuhiko Sugawara, Nobuhisa Akamatsu, Junichi Kaneko,
Sumihito Tamura, Taku Aoki, Yoshihiro Sakamoto, Kiyoshi Hasegawa,
Norihiko Kokudo*

Department of Surgery, University of Tokyo, Japan

Critical shortage of organs available still remains the main problem of liver transplantation for hepatocellular carcinoma (HCC). Milan criteria (MC) have been the most influential in this aspect. However, several groups have now expanded the MC to some extent (5, 6, or more tumors, while others expanding the maximal size acceptable, to 6.5 cm, 8 cm, or larger).

At University of Tokyo, we have applied Living donor liver transplantation (LDLT) to HCC exceeding the MC in selected cases. The current guideline for HCC is up to 5 nodules with a maximum diameter of 5 cm (5-5 rule). Until the end of 2012, 125 patients with HCC underwent LDLT. Of these, 118 (94%) were within Tokyo 5-5 rule criteria and 109 (87%) were within MC (imaging study). Seventy-seven (60%) presented with hepatitis C virus infection. Cumulative rates of recurrence at 5 years within and beyond Tokyo 5-5 rule or MC were 9% and 43% ($P = 0.01$ by log-rank test). Overall survival at 5 years after transplantation were 76% (median follow up period 84 months). HCC recurred in 11 patients.

As in the other studies from Asia countries, our study warrants continuing performance of LDLT for HCC exceeding the MC. In regions where organ donation from deceased donor is limited, LDLT has remained as the only realistic option. Under such settings limitations based on the argument of public equity may require flexible adjustments. How much to expand on what grounds in LDLT, deserves further discussions.

Speaker's Curriculum Vitae

Name Ken Shirabe
Institution Department of Surgery and
Science, Kyushu University



1986 Graduated from Kyushu University, Japan
1990–1992 Research fellow, Department of Surgery, University of Minnesota
2012 Vice professor, Department of Surgery and Science, Kyushu
University

MW02-4**Extended Criteria for Liver Transplantation in the Patients with Hepatocellular Carcinoma – Kyushu University Experience –**

Ken Shirabe, Tomoharu Yoshizumi, Toru Ikegami, Mizuki Ninomiya, Tomohiro Iguchi, Yoshihiko Maehara

Department of Surgery and Science, Kyushu University, Japan

Backgrounds: Milan criteria (MC) are a gold standard for the candidates of liver transplantation (LT) with hepatocellular carcinoma (HCC). The outcome of patients with HCC within MC after LT has been reported to be good. Nevertheless, some of the patients with HCC beyond MC have survived without HCC recurrence after LT. And in Japan, because of brain death donor shortage, living donor liver transplantation (LDLT) has been performed in most of the patients with HCC. Compared with deceased donor liver transplantation (DDLT), criteria for LDLT would be wide under mutual comprehension between living donor and recipient. We have proposed Kyushu university criteria, based on tumor size and des-gamma-prothrombin (DCP). Kyushu university selection criteria is a tumor size <5 cm or a DCP of <300 mAU/ml. In this symposium, we show the validity of extended criteria and comparison among extended criteria.

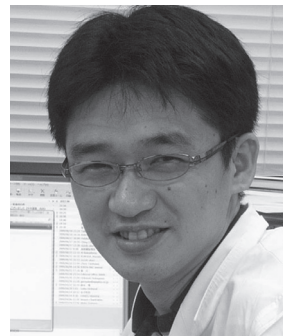
Patients and Methods: One hundred sixty seven patients who underwent LDLT for HCC at Kyushu university hospital. One hundred patients had HCC within MC, and 63 patients had HCC beyond MC. Extended selection criteria, such as Tokyo, Kyoto, up to seven, Japan criteria, and Kyushu university criteria were compared, based on 5 year survival rates both within and beyond criteria in 63 patients with HCC beyond MC, and rates of the patients within the criteria.

Results: The 5 year survivals (%) within and beyond Tokyo criteria were 82.5 and 52.0 ($p = 0.0909$), those within and beyond Kyoto criteria were 81.6 and 45.0 ($p = 0.0132$), those within and without up to seven criteria were 95.0 and 50.8, those within and beyond Japan criteria were 71.5 and 61.8 ($p = 0.4399$) and those within and beyond Kyushu univ. criteria were 70.4 and 20.0 ($p = 0.0041$). Kyoto and Kyushu criteria stratified the patients with HCC beyond MC. The rates of the patients within extended criteria were as follows: Kyushu Univ. >Kyoto>Tokyo>Japan>up to seven.

Conclusion: Extended criteria should be compared, based on both good stratification and rates patients within criteria and the good criteria would provide maximization of benefits for patients with HCC.

Speaker's Curriculum Vitae

Name Koichi Matsuda
Institution Laboratory of Molecular Medicine,
Human Genome Center, Institute of
Medical Science, The University of
Tokyo



Education & Degrees:

1994 MD, graduated from the University of Tokyo
1994–1999 Department of Orthopaedic Surgery, University of Tokyo
1999–2003 PhD, graduate school of medicine, University of Tokyo
2003–2004 Postdoctoral Research Fellow, Baylor College of Medicine
2004– Assistant Professor, Laboratory of Molecular Medicine,
The University of Tokyo
2009– Associate Professor, Laboratory of Genome Technology,
The University of Tokyo

Research Interest:

Genetics, oncology, p53.

MW03-1**Impact of Genetic Variations on Chronic Viral Infection and Prognosis***Koichi Matsuda*

Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Japan

The recent progress in genome-wide association studies (GWAS) has led to the identification of many loci associated with common diseases as well as with quantitative traits. We here present GWAS for HCV-induced liver cirrhosis/hepatocellular carcinoma as well as chronic hepatitis B.

To identify the genetic susceptibility factor(s) for hepatitis C virus-induced hepatocellular carcinoma (HCV-induced HCC), we conducted GWAS using 432,703 autosomal SNPs in 721 HCV-induced HCC cases and 2,890 HCV-negative controls of Japanese origin. TOP eight SNPs ($P < 1 \times 10^{-5}$) in the GWAS were further genotyped in 673 cases and 2,596 controls. We found a novel locus in the 5' flanking region of MICA on 6p21.33 (rs2596542, $P = 4.21 \times 10^{-13}$, odds ratio = 1.39) to be significantly associated with HCV-induced HCC. We also found that risk allele of SNP rs2596542 was associated with lower soluble MICA levels in HCV-induced HCC patients ($P = 1.38 \times 10^{-13}$), suggesting the protective role of MICA for HCC progression. Using similar strategy, we also found that two SNPs, rs910049 and rs3135363, were significantly associated with the progression from CHC to LC ($P = 9.15 \times 10^{-11}$ and 1.45×10^{-10} , respectively).

We also conducted a two-step genome-wide association study using 786 Japanese chronic hepatitis B patients and 2,201 controls and identified a significant association of chronic hepatitis B with 11 SNPs in a region including *HLA-DPA1* and *HLA-DPB1* genes. These associations were validated in two Japanese and one Thai cohorts consisting of 1,300 cases and 2,100 controls (combined $P = 6.34 \times 10^{-39}$ and 2.31×10^{-38} , OR = 0.57 and 0.56, respectively). Subsequent analyses revealed disease susceptible haplotypes (*HLA-DPA1**0202-*DPB1**0501 and *HLA-DPA1**0202-*DPB1**0301, OR = 1.45 and 2.31) and protective haplotypes (*HLA-DPA1**0103-*DPB1**0402 and *HLA-DPA1**0103-*DPB1**0401, OR = 0.52 and 0.57). These findings elucidated the strong impact of genetic factors on HBV and HCV related diseases.

Speaker's Curriculum Vitae

Name Tomomi Kogiso
Institution Departments of Internal Medicine
and Gastroenterology, Tokyo
Women's Medical University



Education:

Apr 1991–Mar 1997 Tokyo Women's Medical College, Tokyo, Japan

Affiliation:

Apr 1997–present Tokyo Women's Medical University

Work Experience:

Aug 2009–present Tokyo Women's Medical University,
Institute of Gastroenterology (assistant)
Aug 2006–Aug 2009 Dept. of Cellular & Molecular Medicine in University of California,
San Diego, Howard Hughes Medical Institute (HHMI)
Jun 2006–Sep 2006 Tokyo Women's Medical University, Institute of Gastroenterology
(assistant)
Jun 2003–May 2006 International Medical center of Japan
Jun 2001–May 2003 Tokyo Women's Medical University, Institute of Gastroenterology
(assistant)
Jun 2000–May 2001 Saitama Municipal Hospital
Jun 1999–May 2000 Shiseikai 2nd Hospital
Apr 1997–May 1999 Tokyo Women's Medical University, Institute of Gastroenterology
(resident)

Certificates:

Aug 2013 Certificated by the Japan Society for Transplantation
Jan 2012 Certificated by the Japanese Society of Gastroenterology
Apr 2011 Board Certified Hepatologist of the Japan Society of Hepatology
Dec 2002 Certificated by the Japanese Society of Gastroentero-endoscopy
Sep 2002 Certificated by the Japanese Society of Internal Medicine (licensed)
Apr 1997 Medical Doctor

Award:

2013 Takako Satake Scholarship Grant at Tokyo Women's Medical University
2011 Nakayama Cancer Research Institute Scholarship
2011 Itoe Okamoto Scholarship Grant at Tokyo Women's Medical University
2010 Hisako Yamakawa Award at Tokyo Women's Medical University
2006 Mochida Memorial foundation for Medical and pharmaceutical research Schol-
arship Grant
2006 Shiseikai Scholarship Grant
2006 Young Investigator's Bursary for the EASL (European Association for the Study
of the Liver):
2003 Young Investigator Travel Award in American Association for the Study of Liver
Diseases (AASLD)

MW03-2**Molecular Mechanisms Underlying the Development of Hepatocellular Carcinoma (HCC)***Tomomi Kogiso, Etsuko Hashimoto*

Departments of Internal Medicine and Gastroenterology, Tokyo Women's Medical University, Japan

According to the International Agency for Research on Cancer GLOBOCAN project 2008, hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer mortality worldwide. Its incidence is expected to increase, so an analysis of the molecular mechanisms underlying carcinogenesis in HCC is required to identify its molecular targets. HCC is a heterogeneous malignancy, and the progression of HCC is a complex and multistep process. The activation of carcinogenic pathways (e.g., oncogenes, growth factors and their receptors, hepatocyte growth factor, telomerase, microRNAs), reactivation of developmental pathways, and inactivation of tumor suppressive pathways are involved in the development of HCC. However, more than 40% of HCCs are clonal, and some HCCs are thought to arise from cancer stem cells. The molecular mechanisms involved in the induction of carcinogenesis and the development of HCC are still largely unknown.

Transforming growth factor- β (TGF- β) is a multifactorial cytokine and a tumor suppressor. We previously reported that TGF- β induced apoptosis in HCC cells via the induction of p21 and p38 MAPK. In addition, the expression of Wee1 kinase, an important negative regulator of the G2/M phase that acts by phosphorylating Cdc2, was downregulated in TGF- β -treated cells. We observed that HCC cells became resistant to TGF- β during long-term culture. However, TGF- β has contradictory effects on HCC cells, as it was recently shown to promote HCC. It is thought that, in this case, TGF- β was activated by stem cells and associated with the carcinogenesis. Therefore, TGF- β is thought to be a therapeutic target in HCC. A TGF- β receptor kinase inhibitor has been tested clinically and was shown to improve patient survival rates.

Here, we report molecular mechanisms in the TGF- β signaling pathway that underlie carcinogenesis in HCC.

Speaker's Curriculum Vitae

Name Pei-Jer Chen
Institution Professor, Graduate Institute of
Clinical Medicine, National Taiwan
University and Hospital



Professor Chen was appointed Director of the Hepatitis Research Center at the National Taiwan University Hospital in Taipei in 2001–2003, and now the faculty for Graduate Institute of Clinical Medicine, National Taiwan University. His research interests focus on the molecular virology of hepatitis viruses, and the genetic and genomic study of hepatocellular carcinoma. Professor Chen's clinical research covers the natural history of chronic viral hepatitis and hepatocellular carcinoma, and also explores and conducts new therapies and trials for both diseases. He was the President of Taiwan Association for Study of the Liver (TASL) from 2012 to 2013.

From 2001 to 2006, he was a member of the editorial board of the journal *Hepatology* and reappointed since year 2010–2011. In 2000, Professor Chen was awarded the International Research Scholar in Infectious Diseases by the Howard Hughes Medical Institute for a period of five years. He has been elected into Academia Sinica in year 2006. He has published over 500 articles in the areas of hepatitis and hepatocellular carcinoma.

MW03-3**Implications for Genomics Sequencing in Target Therapies and Chemoprevention for HCC***Pei-Jer Chen*Graduate Institute of Clinical Medicine and Hepatitis Research Center,
National Taiwan University and Hospital, Taipei, Taiwan

The nature of genomic mutations in HCC and its off-spring or progenitors have been recently addressed by next-generation sequencing. We present the analysis of the evolution of tumors in a case of hepatocellular carcinoma (HCC) and its recurrence, and in other cases from adenoma to HCC and 9 different sections from three tumors and 7 more sections from the adjacent non-tumor tissues. Selected sections were subjected to exon as well as whole-genome sequencing. Putative somatic mutations were then individually validated across all 9 tumor and 7 non-tumor sections. These somatic mutations define the evolutionary lineages among tumor cells.

Separate evolution and expansion of these lineages were recent and rapid, each apparently having only certain lineage-specific protein-coding mutations (foreground mutations), though they all shared the same genomic alterations (background mutations). Hence, by a cell-population genetic definition, this approach identified two classes of genomic mutations. These distinct functions of mutations at different stages may reflect the genetic interactions underlying tumor growth.

The results indicated a very high heterogeneity for the genomic alterations in many sublineages in a single HCC, an observation challenging a single, effective target therapy. This finding calls for the necessity of universal cytotoxic therapies and also promote the direction of chemoprevention or active eradication of carcinogens as the major paths for HCC control.

Speaker's Curriculum Vitae

Name Naoshi Nishida, MD, PhD
Institution Associate Professor, Department of
Gastroenterology and Hepatology,
Kinki University School of Medicine



Educational History:

1989–1993: Kyoto University, Graduate School of Medicine, Kyoto, Japan
1979–1985: Osaka Medical School, Osaka, Japan

Employment History:

2011–present: Associate Professor, Kinki University School of Medicine, Dept. of Gastroenterology and Hepatology
2007–2011: Lecturer/Assistant professor, Kyoto University School of Medicine, Dept. of Gastroenterology and Hepatology
2004–2006: Research Associate, Baylor University Medical Center, Division of Gastroenterology
1997–2004: Assistant professor, Kyoto University School of Medicine, Dept. of Medicine and Clinical Science

Honors and Awards:

1993 Investigator Award of the Japan Society of Hepatology
2008 CHUGAI Award
2009 Presidential Prize of the 45th Annual Meeting of Japan Society of Hepatology

MW03-4**Oxidative Stress and Epigenetic Instability in Human Hepatocarcinogenesis***Naoshi Nishida, Masatoshi Kudo*

Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Japan

Chronic hepatitis C (CHC) triggers oxidative stress and contributes to the emergence of hepatocellular carcinoma (HCC). We previously reported that tumor suppressor gene (TSG) methylation is a critical factor during the early stages of hepatocarcinogenesis. Here, we clarify the association between oxidative stress and epigenetic alterations during hepatocarcinogenesis. We examined DNA oxidation and methylation profiles in 128 liver biopsy samples from CHC patients. The DNA oxidation and methylated TSG numbers were quantified using immunohistochemical analysis of 8-hydroxydeoxyguanosine (8-OHdG) and quantitative PCR for 11 TSGs, respectively. The quantitative chromatin immunoprecipitation-PCR (ChIP-qPCR) assay in HCC cell line and fetal liver cells treated with H_2O_2 was used to quantify trimethyl-H3K4, acetylated-H4K16 (an active chromatin marker), trimethyl-H3K27 (a repressive chromatin marker) and 8-OHdG. We analyzed 30 promoters of 25 different TSGs by qPCR. The high levels of 8-OHdG was the only variable that was significantly associated with the increased number of methylated TSGs in CHC ($p < 0.0001$). The ChIP-qPCR revealed that after H_2O_2 treatment of the cell lines, the 8-OHdG-bound promoters showed a modification from an active chromatin (trimethyl-H3K4 and acetylated-H4K16 dominant) to a repressive chromatin (trimethyl-H3K27 dominant) status. We conclude that oxidative stress alters the chromatin status, which leads to abnormal methylation of TSGs, and contributes to hepatocarcinogenesis in CHC patients.

Speaker's Curriculum Vitae

Name Shinji Tanaka
Institution Associate Professor,
Department of Hepato-Biliary-
Pancreatic Surgery,
Tokyo Medical and Dental
University



Education and Training:

1988	MD, Cum laude, Faculty of Medicine, Kyushu University
1988–1989	Resident, Department of Surgery II, Kyushu University Hospital
1989–1990	Medical Staff in Surgery, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital
1990–1993	Doctor Course, Graduate School of Medicine, Kyushu University
1993	PhD, Doctor of Medical Science
1993–1994	Assistant Professor, Department of Virology, Faculty of Medicine, Kyushu University
1994–1996	Research Fellow, Cancer Center, Massachusetts General Hospital and Harvard Medical School
1996–1999	Assistant Professor, Department of Surgery, Medical Institute of Bioregulation, Kyushu University
1999–2004	Assistant Professor, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University
2004–2005	Surgical Staff, Department of Gastroenterological Surgery, National Kyushu Cancer Center
2005–2006	Assistant Professor, Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University
2006-date	Associate Professor, Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University

Awards:

1996	Yong Investigator Award, American Association for the Study of Liver Diseases
1998	Medical Research Award, Japan Medical Association
1999	Incitement Award, Japanese Cancer Association
1999	Award of Fukuoka Medical Society
2004	Award for Cancer Research, International Symposium on Cancer Research and Treatment
2006	JSPS Prize, Japan Society for the Promotion of Science
2007	IRPC "Eminent Scientist of the Year" Gold Medal, International Research Promotion Council
2012	JCA-Mauvernay Award, Japanese Cancer Association
2013	JSGS Award Science of the Year 2013, The Japanese Society of Gastroenterological Surgery

MW03-5**Novel Molecular Targets and Therapeutic Combinations in Hepatocellular Carcinoma; Rationale and Significance***Shinji Tanaka*

Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University, Japan

Accumulated evidences suggest that multiple oncogenic pathways activate the carcinogenesis and progression of cancers. Since much more complicated molecular interactions might function *in vivo*, the comprehensive analysis using clinical tissue samples is of growing significance in the therapeutic application. We have analyzed more than 1,000 clinical samples from surgically resected tissue to identify molecular biomarkers and therapeutic targets for advanced cancers including hepatocellular carcinoma (HCC). Gross vascular invasion as well as gross morphology of tumor nodules is known as the prognostic indicator of patients with HCC. According to DNA microarray and network analysis on clinical samples of HCC, we identified the mitotic kinase and stemness-related molecule as the distinct biomarker of vascular invasion and tumor morphology, respectively. *In vitro* treatment with the selective inhibitor of the mitotic kinase induced cell polyploidy, and resulted in death by mitotic catastrophe. Noteworthy, we found an anti-apoptotic protein was specifically overexpressed in the polyploid HCC cells after inhibition of the mitotic kinase. Combination treatment using the inhibitors of mitotic kinase and anti-apoptotic protein induced synergistically cellular apoptosis and growth inhibition. *In vivo* studies using tumor xenografts of human HCC cells revealed the combination therapy of mitotic kinase and anti-apoptosis inhibitors induced significantly intratumoral apoptosis and remarkable anti-tumor effects without severe adverse effect, compared to the monotherapy.

Since the stem cell markers CD133 and CD13 were increased after treatment with anti-cancer drug 5-FU, we evaluated the combination effects of the stemness-targeted inhibitor with 5-FU in HCC cells. Combination treatment of stemness inhibitor and 5-FU showed not only potent cytotoxicity *in vitro*, but also significant regression of tumors *in vivo*. In orthotopic liver xenograft models, the combination therapy dramatically decreased the tumor volume. Based on clinical and biological assessments, the rationale of therapeutic combinations targeting additive oncogenes might lead a promising novel approach for the treatment of human HCC.

Speaker's Curriculum Vitae

Name Peter Robert Galle, MD, PhD
Institution University Medical Center Mainz
Position Direktor 1st Medical Department



Dr. Galle majored in internal medicine at the Universities of Berlin and Marburg/Germany, Hammersmith Hospital, London/UK and University of Texas/USA and received his MD degree from Marburg University and PhD degree from Heidelberg University.

Initially he held a position as postdoctoral fellow in Molecular Biology at the Centre for Molecular Biology Heidelberg working on the replication of hepatitis B viruses. Afterwards he completed his residency in Internal Medicine and Gastroenterology at the University Hospital of Heidelberg. In 1998 he became Director of the I. Medical Department in Mainz and from 2005–2008 he held the CEO position of Mainz University Hospital.

He is member of several national and international societies such as the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), and serves as Co-editor for the Journal of Hepatology and is on the Editorial Boards of several other Journals. He is member of the Executive Board and President of the International Liver Cancer Association (ILCA).

His research has focused on elucidating important aspects of apoptotic cell death in the liver, immune escape of tumour cells, and preclinical and clinical research in HCC. He was awarded several prizes, amongst others the prestigious Tannhauser award, the highest prize of the German Society for Digestive Diseases. He has published more than 350 peer-reviewed papers.

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MW03-6

Signal Transduction and New Molecular Targets in Hepatocellular Carcinoma

Peter R. Galle

1st Department of Medicine, University Medical Center, Mainz, Germany

The molecular processes that drive the transformation of normal hepatocytes into malignant cells, such as those occurring during the development of hepatocellular carcinoma (HCC), are complex. Two early pathogenetic steps have been identified. Firstly, in most cases, liver cirrhosis presents with a precancerous lesion following viral hepatitis infection, excessive alcohol consumption or exposure to environmental toxins. Secondly, mutations occurring in one or more genes accumulate, either in the context of chronic inflammation or as the result of direct DNA damage. This results in aberrations in several cellular signalling pathways that are important for tumour angiogenesis and the survival and proliferation of tumour cells.

The knowledge of signalling pathways controlling proliferation and angiogenesis has – after years of therapeutic nihilism – resulted in the development of the multikinase inhibitor sorafenib as the first agent to demonstrate a significant improvement in the survival of patients with advanced hepatocellular carcinoma (HCC). However, survival benefits on sorafenib treatment remain modest in clinical practice and further clinical trials on other targeted agent so far failed to demonstrate a relevant clinical benefit in phase III trials in first- or second-line settings. In addition, according to a recent press release sorafenib failed in the adjuvant setting.

One explanation for this detension in the development of therapeutical strategies in HCC ist the general lack of available tumor tissue which would help to identify subgroups of patients benefitting from novel strategies. This is in contrast to other tumors such as lung cancer where molecular subgrouping is already reality.

Given the current problems in successfully treating HCC, we need to aim for novel therapeutic strategies. Besides the characterization of predictive signatures to subgroup patients with HCC, understanding and unravelling the characteristics of stem cell biology in HCC may pave the road to such novel strategies.

The presentations will discuss signal transduction and new molecular targets in HCC.

Speaker's Curriculum Vitae

Name Yasushi Nagata
Institution Professor and Chairman,
Department of Radiation Oncology,
Hiroshima University, Graduate
School of Biomedical and Health
Sciences



Education:

MD, Kyoto University, Faculty of Medicine, 1982
PhD, Kyoto University, 1990

Major Subjects:

Radiation Oncology (Treatment planning, Stereotactic Radiotherapy)

Professional Experience:

1982–1983 Junior Resident of Radiology, Kyoto University Hospital
1990–1994 Instructor, Dept. of Therapeutic Radiology, Kyoto University
1993–1994 Visiting Assistant Professor, Radiation Biology Section, Dept. of
Therapeutic Radiology, University of Minnesota
1994– Assistant Professor, Dept. of Therapeutic Radiology, Kyoto
University
2000–2008 Associate Professor, Vice-chairman, Dept. of Therapeutic Radi-
ology, Kyoto University
2008.1– Professor, Div. of Radiation Oncology, Hiroshima University
Hospital
2009.4– Professor and chairman, Dept. of Radiation Oncology,
Hiroshima University, Graduate School of Biomedical and Health
Sciences

Award and Honors:

1996 Umegaki Award (JASTRO)
2006 Abe Award (JASTRO)

Board Certification:

Radiation Oncology (1989)

MW04-1**Stereotactic Body Radiation Therapy (SBRT) for Hepatocellular Carcinoma (HCC)***Yasushi Nagata, Tomoki Kimura*

Department of Radiation Oncology, Hiroshima University, Japan

Purpose: Stereotactic body radiation therapy (SBRT) is a new technique to focus radiation to the focal tumor. This technique is widely available for lung cancer, however for hepatocellular carcinoma (HCC) has yet to become commonplace. We actively use this technique at our hospital when surgery or radiofrequency ablation (RFA) are not indicated. This study aimed to investigate the treatment outcomes of SBRT for HCC.

Materials & Methods: Subjects comprised 83 HCC patients (99 lesions) who underwent SBRT at Hiroshima University Hospital from March 2002 to December 2012. Using eight-field non-coplanar radiation with 6–10 MV X-ray beams, SBRT was performed on peripheral type cases with an isocenter dose of 4 × 48 Gy and that on central type cases (mainly hepatic portal region) with an isocenter dose of 8 × 60 Gy. Transcatheter arterial embolization (TACE) was also used in 77 patients.

The following items were examined.

- 1) Dose irradiating 95% of the planning target volume (PTV) (D95)
- 2) Overall survival, disease-free survival, and local control rates
- 3) Adverse events
- 4) Analysis of factors affecting overall survival and local control rates

Results: The median observation period was 34 months (range: 4–96 months), and the median age of the patients was 78 years (range: 46–90 years).

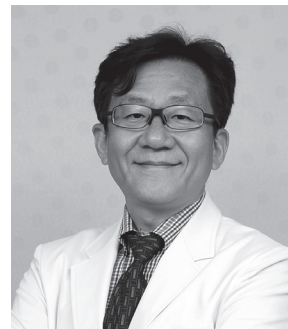
- 1) The median D95 value was 45.7 Gy (range: 37.4–59.3 Gy).
- 2) The two-year overall survival, local recurrence-free survival, and local control rates were 72.9% (95% CI; 62.2%–83.5%), 37.6% @ 2 years (95% CI; 26.4%–48.8%) and 98.9% (95% CI; 96.7%–100%), respectively. The median survival period was 32 months.
- 3) Evaluation with CTCAE ver. 4.0 indicated that the proportion of adverse events of Grade 3 or higher at 6–12 months was observed in 21/83 cases (25.3%). In one of these cases, Grade 4 thrombopenia was observed. No gastrointestinal ulcers or perforation were seen. Adverse events of Grade 3 or higher were significantly more common in Child–Pugh classification Class B cases ($p < 0.001$).
- 4) Multivariate analysis was performed using the log-rank test, with results indicating that the overall survival rate was significantly more favorable in Child–Pugh classification Class A cases ($p = 0.0046$).

Discussion: Treatment outcomes at our hospital were favorable, with a two-year local control rate of 98.9%, suggesting that SBRT is a possible option for local treatment when surgery or RFA is not indicated. Furthermore, although the rate of adverse events of Grade 3 or higher was 25.3%, considering that this was roughly identical to the rates indicated in various reports in the literature and that most of these were recurrence cases had already undergone another treatment such as surgery or RFA, we believe that SBRT can be performed relatively safely. However, special attention should be paid to the patients with Child–Pugh classification Class B because adverse events of Grade 3 or higher were noted in these cases.

Conclusion: This study showed that SBRT for HCC can achieve a high local control rate relatively safely, suggesting that it could become a treatment option for patients for whom treatment with surgery or RFA is difficult. In the future, we plan to conduct a multicenter prospective study regarding the efficacy of SBRT for untreated solitary primary HCC.

Speaker's Curriculum Vitae

Name Hee Chul Park, MD, PhD
Institution Associate Professor,
Department of Radiation Oncology,
Samsung Medical Center,
Sungkyunkwan University School
of Medicine



Hee Chul Park studied Medicine at Yonsei University College of Medicine and graduated in 1992. Following this, he completed a clinical fellowship in Chosun University Hospital followed by a lecturer at Severance Hospital and subsequently completed his Master's and PhD degree from Yonsei University.

Dr. Hee Chul Park is currently an Associate Professor of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea. Prior to his current position, he has been a visiting scientist in Department of Experimental Radiotherapy, MD Anderson Cancer Center, Houston, USA and Honorable Visiting Instructor in Department of Radiology, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

He has many honors and awards to his credit including KLCSC Academic Research Funding Award (The 15th Annual Meeting 2012) and KOSRO/ROJ Excellent Paper Award (The KOSRO Spring Symposium 2013). He has published 58 articles in international peer-reviewed journals. He has also delivered 57 talks at various international congresses.

MW04-2

Recent Developments and Future Indications in Radiotherapy for Hepatocellular Carcinoma

Hee Chul Park

Department of Radiation Oncology, Samsung Medical Center,
Sungkyunkwan University School of Medicine, Korea

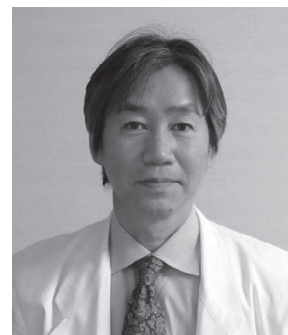
The role of radiotherapy in practice is mainly palliative. According to the Practice Guidelines for Management of Hepatocellular Carcinoma (2009) developed by the Korean Liver Cancer Study Group and the National Cancer Center, Korea, radiotherapy can be applied for 1) refractoriness to trans-catheter hepatic arterial chemo-embolization, 2) portal vein tumor thrombosis, and 3) palliative therapy to reduce the symptoms caused by hepatocellular carcinoma.

Radiotherapy is one of the most rapidly developing fields of medical research. Recent advances in intensity-modulated radiotherapy, image-guided radiotherapy, and respiratory-gated radiotherapy technologies have enabled more accurate and precise radiation delivery for the treatment of hepatocellular carcinoma. Proton therapy is also emerging as a candidate therapy for ablative measures for patients ineligible for other curative local therapies. Due to recent advances in radiotherapy technologies, radiotherapy for hepatocellular carcinoma has been evolving into stereotactic ablative radiotherapy, which delivers an ablative dose of radiation in 1 to 4 sessions. Clinical series have confirmed that it is safe in Child-Pugh A patients and local control is sustained. The possibility for performing phase 3 randomized clinical trials involving the radiotherapy modality has increased with those advances.

Not merely palliative, the role of radiotherapy in the treatment of hepatocellular carcinoma will be expanded to potentially curative therapy in patients who are ineligible for other curative local therapies.

Speaker's Curriculum Vitae

Name Toshiyuki Okumura
Institution Proton Medical Research Center,
University of Tsukuba



Work Experience:

1983 Apr–1986 Aug	Resident in Radiology, University Hospital of Tsukuba
1986 Sep–1986 Nov	Visiting doctor in Head & Neck Surgery, National Cancer Center
1986 Dec–1988 June	Resident in Radiation Oncology, University Hospital of Tsukuba
1988 July–1992 Mar	Chief radiation oncologist, Ibaraki Prefectural Hospital & Cancer Center
1992 Apr–2000 Mar	Assistant Professor in Proton Medical Research Center, University of Tsukuba
2001 Apr–2007 Oct	Chief radiation oncologist, Ibaraki Prefectural Hospital & Cancer Center
2007 Nov–2008 Nov	Director, Dep. of Radiation Oncology, Ibaraki Prefectural Hospital & Cancer Center
2008 Dec–2010 Nov	Associate professor, Proton Medical Research Center, University of Tsukuba
2010 Dec–present	Clinical professor of Tsukuba University Hospital

Academic Activities:

The Japan Society of Clinical Oncology
The Japan Radiological Society (JRS)
The Japanese Society for Therapeutic Radiology and Oncology (JASTRO), (Councilor)
American Society of Therapeutic Radiology (ASTRO), International member
European Society of Therapeutic Radiology (ESTRO), International member
Particle Therapy Cooperative Group (PTCOG)
The Japan Society of Medical Physics (JSMP), (councilor)

Mr. Okumura is Associate professor in Proton Medical Research Center of Tsukuba University, and Clinical professor in Tsukuba University Hospital. He is a radiation oncologist and has been engaged in proton beam therapy of Tsukuba University since 1992. His recent research areas include treatment of liver cancer, lung cancer, skull base tumors, and cerebral arteriovenous malformation.

MW04-3

Particle Radiotherapy

Toshiyuki Okumura¹, Nobuyoshi Fukumitsu¹, Masashi Mizumoto¹, Hitoshi Ishikawa¹, Kuniaki Fukuda², Masato Abe², Kiyoshi Fukunaga³, Koji Tsuboi¹, Takeji Sakae¹, Nobuyuki Ohkohchi³, Hideyuki Sakurai¹

¹Proton Medical Research Center, University of Tsukuba, Japan;

²Department of Gastroenterology, University of Tsukuba, Japan;

³Department of Surgery, University of Tsukuba, Japan

Radiotherapy has played a limited role in treatment of hepatic malignancies due to the low whole-liver tolerance of ionizing radiation. However, high-dose radiotherapy can safely be applied, provided that a substantial portion of the normal liver is preserved. Particle beams, such as proton and carbon ion beams with finite penetration, can create ideal dose distribution to preserve the functioning liver, effectively. Integrated techniques combining fiducial marker placement, image-guided radiotherapy, and compensation of target motion is mandatory for liver tumors to reduce their internal target volume. Prescribed doses for particle beams are usually much higher than those for conventional photon therapy. In our proton beam facility, the doses are determined depending on tumor location, for example, 66GyE with 10 fractions for peripheral tumors, 72.6GyE with 22 fractions for tumors involving porta hepatis. In contrast, significantly smaller number of fractions, such as four or two, is employed for carbon ion therapy.

The major difference between proton and carbon ion beams lies in lateral penumbra of beams and relative biological effectiveness. Clinical results of proton and carbon ion therapy were comparable despite of those differences. Most of the clinical data reported so far are of treatment of hepatocellular carcinoma (HCC). HCC accounts for between 85% and 90% of primary liver cancers, and usually follows liver cirrhosis. The local progression-free and overall survival rates at 3 years are reported to be approximately 85–90% and 50%, respectively. Treatment outcome is less affected by tumor location, tumor vascularity, nor tumor size. And those features are the advantage of particle therapy over other local therapies. Patient's liver function is always an important prognostic factor. Acute toxicity is minimal and late toxicity greater than grade 3 is rare. Particle therapy is a feasible and effective treatment for hepatic malignancies.

Speaker's Curriculum Vitae

Name Jinsil Seong, MD, PhD
Institution Professor,
Department of Radiation Oncology,
Yonsei University College of
Medicine



Professor Jinsil Seong currently works at Department of Radiation Oncology, Yonsei University College of Medicine, Seoul. Prior to her current position, she has been a Visiting Scientist in Department of Experimental Radiotherapy, MD Anderson Cancer Center, Houston, USA. She graduated from Yonsei University College of Medicine, Seoul and subsequently completed her PhD degree from Yonsei University, Seoul.

Professor Seong is a former President of Yonsei Liver Cancer Study Group and also a member of various national and international societies including International Liver Cancer Association, Korean Liver Cancer Study Group, European Society for Therapeutic Radiology and Oncology and American Society for Therapeutic Radiology and Oncology. She served as a member of the Editorial Board of International Journal of Radiation Oncology Biology Physics for the past 10 years. Currently she is a council member of Asian Clinical Oncology Society as well as Asia Pacific Primary Liver Cancer Expert Meeting. She is also working as a consultant in International Atomic Energy Agency. She has been awarded many times for her credit including Korean Cancer Association Distinguished Scientific Award (2012), Best Presentation Award (bronze) in 2nd Asia Pacific Primary Liver Cancer Expert Meeting (2011) and Young Investigator Award in International Congress of Liver Disease (2004). She has published 93 articles in non-SCI listed journals and 100 articles in SCI listed journals. She has also delivered 106 talks at major national and international congresses. Research interest is "Radiotherapy of HCC" in clinical approach as well as in translational research.

MW04-4

Targeted Radiotherapy for Hepatocellular Carcinoma

Jinsil Seong

Radiation Oncology, Yonsei University Medical College, Korea

Three major modalities involving surgery, radiotherapy, and chemotherapy have long contributed to cancer therapy. For the advanced disease, combination of two or all of those modalities has been recognized as the best approach, establishing a concept of multimodality treatment of cancer. This approach has been successful in most solid cancers but not in hepatocellular carcinoma (HCC), particularly in the use of radiotherapy. This wrong notion had come from a clinical observation in the past, poor tumor control with high toxicity, which adopted whole liver radiation even with the dose less than tumoricidal level.

Current notion in radiotherapy of HCC is based on 2 revolutionary changes; one is conceptual change in radiotherapeutic coverage of volume from whole liver to local tumor area and the other is remarkable development of radiotherapy technology. Through computerized planning system dose-volume statistics are informed for both tumor and normal tissues so that tumor control and toxicity can be predicted even before the radiotherapy started. Liver as a moving organ, another obstacle, has also been overcome either by minimizing the motion or by tracking/gating.

Investigation is going further to overcome inherent radioresistance of tumor. Although this approach remains investigational in HCC, identification of radioresistant subvolumes through molecular imaging (biological targeting) followed by precise delivery of focal high dose radiation on such subvolumes (physical targeting) is currently possible at a basic level. This field is rapidly progressing. Although it doesn't seem easy, it is NOT impossible to achieve.

Speaker's Curriculum Vitae

Name Masayuki Kurosaki
Institution Director, Department of
Gastroenterology and Hepatology,
Musashino Red Cross Hospital;
Adjunct Professor, Tokyo Medical
and Dental University; Assistant
Professor, Yamanashi University



Academic Qualifications:

1995 PhD in Medicine, Tokyo Medical and Dental University
1987 MD in Medicine, Tokyo Medical and Dental University

Working/Teaching Experience:

2014–present, Adjunct Professor, Tokyo Medical and Dental University
2011–present, Assistant Professor, Yamanashi University
2010–present, Director, Department of Gastroenterology and Hepatology,
Musashino Red Cross Hospital
2006–present, Associate Professor, Tokyo Medical and Dental University
2003–2010, Associate Director, Department of Gastroenterology and Hepa-
tology, Musashino Red Cross Hospital
1995–2003, Assistant Professor, Tokyo Medical and Dental University

Professional Membership:

Councilor and fellow of Japan Society of Hepatology
Councilor and fellow of the Japanese Society of Gastroenterology
Councilor and fellow of Japan Gastroenterological Endoscopy Society
Fellow of the Japanese Society of Internal Medicine

Editorial Board:

Present, BioMed Research International
Present, World Journal of Hepatology

Research Activities:

Co-investigator of 6 Study group supported by Ministry of Health, Labour and
Welfare, Japan

LS01-1

Role of Antiviral Therapy in the Total Management of HCC: A Personalized Strategy

Masayuki Kurosaki

Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital; Tokyo Medical and Dental University; Yamanashi University, Japan

HCC risk prediction model revealed that HCC risk reduction by interferon therapy differ by the baseline risk

The rate of successful eradication of hepatitis C virus (HCV) has now reached 90% by using simeprevir, a second generation protease inhibitor, in combination with pegylated interferon and ribavirin. In this era of rapidly evolving therapy, most physicians and patients prefer to wait for even newer direct antiviral agents (DAA) if the risk of HCC development is negligible. An HCC risk prediction model we have built on the basis of factors such as age, platelet, albumin, and AST identified subgroups with a 5-year HCC development rate of 21%, 6%, and 1.5%, respectively. Another short-term HCC prediction model using alpha-fetoprotein (AFP) and platelet divided subgroups with a 2-year HCC development rate of 4% or 0.6%. The incidence of HCC was significantly reduced by the eradication of HCV only in high-risk group. Thus, risk assessment could be used to differentiate patients who benefit from immediate therapy and those who could wait for newer emerging therapy.

Identification of patients who need surveillance for HCC after successful eradication of HCV by antiviral therapy

Highly effective antiviral therapy enables the eradication of HCV in patients at high risk of HCC which may lead to paradoxical increase of HCC after HCV eradication. Multicenter study showed identified that hallmarks of residual risk for HCC was age over 60, male, low platelet counts, and serum AFP >5 ng/ml which may be used to identify candidate for a careful HCC surveillance even after the complete eradication of hepatitis C virus.

Antiviral therapy after the curative loco-regional ablation therapy for HCC

The role of antiviral therapy after the cure of HCC by ablation therapy was studied in another multicenter study. The survival was prolonged in HCC patients with successful HCV eradication. On the other hand, cumulative incidence of HCC recurrence was not reduced by HCV eradication alone but was significantly reduced by normalization of AFP. The role of antiviral therapy for the prevention of HCC recurrence needs further investigation.

Speaker's Curriculum Vitae

Name Josep M. Llovet, MD
Institution Professor of Research, ICREA, BCLC Group, Liver Unit, Hospital Clínic Barcelona; Professor of Medicine, Director, Division of Liver Diseases, Mount Sinai School of Medicine, New York



Josep M. Llovet is **Professor of Research-ICREA** in the BCLC Group, Liver Unit, IDIBAPS-Hospital Clínic of Barcelona (Spain), **Director of the HCC Program and Professor of Medicine** at the Mount Sinai School of Medicine, New York University (USA). Professor Llovet obtained his degree in Medicine and Surgery from the University of Barcelona in 1986 and his PhD from the Autonomous University of Barcelona in 1995.

Professor Llovet is **President of the International Liver Cancer Association (ILCA)** and Chairman of the European Clinical Practice Guidelines of management of liver cancer (EASL-EORTC). He has published more than 180 articles in peer-reviewed journals such as *New England Journal of Medicine*, *Nature Genetics*, *Lancet*, *Cancer Cell*, *Journal Clinical Investigation*, *Journal of Clinical Oncology*, *Lancet Oncology*, *Gastroenterology* and *Hepatology* (total citations 22,490, total impact factor 1876; h index 67), more than 40 chapters of books, and has delivered more than 400 lectures. He is Senior Editor of *Clinical Cancer Research* and Special Editor of *Gastroenterology* and *Journal of Hepatology*.

During the last 15 years, Dr. Llovet received the AACR-Landon International Award (2009), the International Hans Popper award (2012), Premi Josep Trueta (2013) and is leading international projects with competitive funding from the European Commission (FP7- HEALTH, HEP-TROMIC, 2010) and the US National Institute of Health (R01, 2008). Below, find described the scientific and managerial positions and the main scientific achievements obtained. He has contributed to advancing knowledge in the following areas:

1. Clinical classification of HCC: With the acronym BCLC (Barcelona-Clínic Liver Cancer) classification, first published in Llovet, *Semin Liv Dis* 1999, and then further modified in Llovet, *Lancet* 2003; Llovet, *J Natl Can Inst*, 2008 and Forner, *Lancet* 2012. This classification has been adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.

2. Establishment of chemoembolization as standard of care: In patients with intermediate HCC. Evidence-based establishment through randomized controlled trials [Llovet, *Lancet* 2002] and meta-analysis [Llovet, *Hepatology* 2003] of chemoembolization as standard of care in patients with intermediate HCC. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.

3. Establishment of sorafenib as standard of care: In patients with advanced HCC (Llovet, *New Engl J Med* 2008). This breakthrough achievement establishes sorafenib as first line treatment for advanced HCC, and represents the first identification of survival advantages with systemic treatments. Identified by *Nature Medicine* as the most cited paper in oncology 2008–2010. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.

4. Guidelines of management of HCC: Chair of EASL-EORTC Guidelines, 2012 (*J Hepatol*, 2012, *Eur J Cancer* 2012), and committee member of guidelines of EASL (2001). Leading author of AASLD guidelines for design of clinical trials in HCC (Llovet, *J Natl Cancer Institute*, 2008).

5. Establishment of a molecular diagnosis of HCC: Gene-set (3 genes) based diagnosis of HCC reported in Llovet, *Gastroenterology* 2006, and included in EASL-EORTC guidelines.

6. Proposal of a molecular classification of HCC and ICC: A final proposal of a molecular classification of HCC is based on the results reported in different publications (Wurmbach, *Hepatology* 2007; Hoshida, *New Engl J Med*, 2008, Chiang, *Cancer Res*, 2008; Hoshida, *Cancer Res* 2009, Villanueva, *Gastroenterology* 2011; Sia, *Gastro* 2013, Hoshida, *Gastroenterology* 2013).

7. Identification of drivers of oncogenesis as targets for therapies: Several studies led to the identification of **Akt/mTOR pathway** [Villanueva *Gastroenterology*, 2008], **Ras pathway** [Newell, *J Hepatol* 2009], **EGFR pathway** [Keng, *Nature Biotech* 2009], **IGF pathway** [Tovar, *J Hepatol*, 2011], **Wnt Pathway** [Lachenmeyer, *CCR* 2012], **Notch pathway** [Villanueva, *Gastroenterology* 2012], AEG [Yoo, *J Clin Invest* 2009] and **miRNAs** [Viswanathan, *Nat Genetics* 2009, Toffanin, *Gastroenterology* 2011] as drivers of hepatocarcinogenesis and potential targets for therapies.

LS02-1

Adjuvant Therapies After Resection/Local Ablation in HCC. Summary of the STORM Trial

Josep M. Llovet

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Resection is the mainstay treatment for early HCC in patients with well-preserved liver function, whereas local ablation with radiofrequency is applied in patients with early tumors not suitable for surgical treatments. In the West, this represents around 30–40% of the HCC population. Despite all improvements in pre-interventional imaging techniques and the acquired experience with these therapies, tumor recurrence still plagues most of cases. HCC recurrence complicates 50–70% of patients at 5 years, reflecting either intrahepatic metastases (true recurrences) or the development of *de novo* tumors. It can be determined that 2/3 of recurrences represent intrahepatic metastases undetected by the time of resection, whereas 1/3 are *de novo* HCCs. True recurrences characteristically appear within 2 years after resection, with vascular invasion, poor histological differentiation degree and satellites the main predictive factors. *De novo* tumors characteristically occur late, defined as more than 2 years after resection.

None of the adjuvant treatments tested so far have gained a place as standard therapy in the field. Several strategies have been tested aimed at preventing intrahepatic metastases (chemoembolization/lipiodolization, internal radiation, chemotherapy or adoptive immunotherapy) or *de novo* tumors (retinoids, vit K or interferon). Initial positive results with retinoids or Vit K turned out to be negative when these molecules were tested in large properly-powered randomized studies. The controversial or negative results reported in around 15 randomized trials leave this area as the primary unmet need in the management of liver cancer.

Randomized clinical trials assessing adjuvant therapies after resection or local ablation constitute a priority area of investigation. The primary end-point of these studies should be either prevention of true recurrences or *de novo* HCC, but molecular data might be required to support these definitions. The preventive strategies targeting both types of recurrences are completely different, and the combination of treatments seems the most rational approach. Alternatively, however, TKI aimed at preventing tumor growth and neo-angiogenesis in both types of recurrences have emerged as the suitable candidate drugs. Sorafenib has been the first and only multikinase inhibitor proving survival benefits at advanced stages of the disease. This molecule is able to prevent tumor growth and angiogenesis by blocking VEGF, PDGFR, p38, c-Kit and B-Raf, among others. Theoretically, sorafenib might be able to delay progression of true metastasis, and eventually prevent the occurrence of *de novo* tumors. A phase III trial (STORM trial) comparing sorafenib vs placebo in 1100 patients with complete response to HCC therapies (either resection or local ablation) has been completed. The primary end-point of the study, recurrence-free survival, was not met. Detailed results of this trial will be presented.

Speaker's Curriculum Vitae

Name Riccardo Lencioni, MD, FSIR, EBIR
Institution Professor and Director,
Division of Diagnostic Imaging and
Intervention,
Pisa University School of Medicine



Riccardo Lencioni, MD, FSIR, EBIR, is board certified in Radiology and Gastroenterology. He is Professor and Director of Diagnostic Imaging and Intervention at Pisa University School of Medicine in Pisa, Italy.

Professor Lencioni is one of the world's foremost interventional oncology specialists, known especially for his highly influential work in liver cancer. He has been a leading member of several expert panels developing recommendations for research and clinical management of hepatocellular carcinoma. He has co-authored the white papers *Design and Endpoints in Clinical Trials in Hepatocellular Carcinoma* (2008), *Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma* (2010), and *EASL-EORTC Clinical Practice Guidelines: Management of Hepatocellular Carcinoma* (2012).

Riccardo Lencioni is the Chairman of the World Conference on Interventional Oncology. He is a co-Founder of the International Liver Cancer Association, in which he also acts as the Executive Secretary. He is an Associate Editor of the journal *Liver Cancer* and serves as an editorial board member or reviewer for several other titles.

Riccardo Lencioni has published 175 articles in peer-reviewed international journals indexed in PubMed and numerous chapters in textbooks of interventional radiology, gastroenterology, oncology and surgery. In addition, he has been the editor of seven books. According to the SCOPUS database, citations of his publications currently number in excess of 11,000 with an *h* index of 45. Riccardo Lencioni has been an invited or honorary lecturer at more than 450 international meetings or conferences.

LS02-2**TACE Combination for Intermediate HCC***Riccardo Lencioni*

Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy

An important limitation of any TACE regimens is the high rate of tumor recurrence. Tumor recurrence following TACE is characterised by increased vascular endothelial growth factor (VEGF) production and subsequent angiogenesis. Moreover, TACE increases VEGF expression in the residual surviving cancerous tissue and induces expression of other pro-angiogenic factors, such as hypoxia-inducible factor 1 alpha. Sorafenib, a multi-kinase inhibitor with anti angiogenic and antiproliferative properties, has been shown to prolong median overall survival and median time to radiological progression compared to placebo in RCTs and has become the current standard of care for patients with advanced-stage tumors not suitable for surgical or loco-regional therapies. Based on these findings, combination of TACE with sorafenib would appear as a rational approach. In a prospective, single-center phase II study conducted at the Johns Hopkins University School of Medicine, safety and response of a combined protocol involving sorafenib 400 mg twice per day and TACE with drug eluting bead (DEB-TACE) were assessed in 35 patients. Although most patients experienced at least one grade 3 to 4 toxicity, most toxicities were minor (grade 1 to 2, 83% vs grade 3 to 4, 17%), and preliminary efficacy data were promising. The phase II randomized, double-blind, placebo-controlled SPACE study (Sorafenib or Placebo in Combination with DEB-TACE for Intermediate-Stage HCC) was conducted to evaluate the efficacy and safety of sorafenib in combination with DEB-TACE in patients with intermediate-stage HCC across Europe, North America, and the Asia-Pacific region. Of 452 patients screened, 307 were randomized to sorafenib (n = 154) or placebo (n = 153). The hazard ratio (HR) for TTP was 0.797 (95% CI, 0.588, 1.080; p = 0.072). Median TTP (50th percentile) was 169 days/166 days in the sorafenib and placebo groups, respectively; TTP at the 25th and 75th percentiles (preplanned) was 112 days/88 days and 285 days/224 days in the sorafenib and placebo groups, respectively. There were no unexpected safety findings. The findings of the SPACE study were supported recently published prospective, single-arm, phase 2 studies conducted in Asian patients with unresectable HCC. Nevertheless, the encouraging signal captured by the SPACE trial requires confirmation with data from ongoing phase 3 trials.

Abstracts Poster Session

P01-1

Acyclic Retinoid Augments Apoptosis of Hepatocellular Carcinoma Cells Under Insulin-Resistance Condition

Norihisa Nishimura, Mitsuteru Kitate, Hitoshi Yoshiji, Ryuichi Noguchi, Tadashi Namisaki, Kei Moriya, Kosuke Takeda, Yosuke Aihara, Akitoshi Douhara, Kawaratani Hideto, Fukui Hiroshi

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Background: Insulin resistance (IR) often coexists with chronic liver disease and it correlates with development of hepatocellular carcinoma (HCC). Acyclic retinoid (ACR) has recently been focused on as a new anti-HCC reagent via augmentation of apoptosis. However, less is known whether ACR is effective under IR condition or not. We evaluated anti-cancer effect of ACR under IR-mimic condition in vitro. **Methods:** Huh-7 and HepG2 cells were incubated under low-glucose or IR-mimic (high-glucose and/or insulin) condition with ACR (10 μ M). Cell proliferation and apoptosis were evaluated by RT-PCR. **Results:** IR-mimic condition increased cell proliferation. In this condition, ACR-treatment inhibited proliferation with increase of p21 and caspase3 expression suggesting effective pro-apoptotic effect of ACR. **Conclusions:** Our dataset suggested ACR is effective against HCC under IR condition. This finding supports wide use of ACR on HCC patients.

P01-2

Cold-Inducible RNA-Binding Protein (Cirp) Promotes the Development of Liver Cancer

Toshiharu Sakurai, Norihisa Yada, Tadaaki Arizumi, Satoru Hagiwara, Tatsuo Inoue, Kazuomi Ueshima, Naoshi Nishida, Masatoshi Kudo

Kinki University, Japan

We examined whether cold-inducible RNA-binding protein (Cirp) controls ROS metabolism and development of cancer in mice given thioacetamide (TAA) to induce chronic liver injury. We assessed Cirp expression and function by using wild type (WT) and Cirp-deficient (Cirp^{-/-}) mice and human liver samples. TAA administration enhanced ROS accumulation and apoptosis in the liver, which was attenuated

by Cirp ablation. Cirp was found to enhance IL-6 production in Kupffer cells and activate STAT3 in the liver, leading to attenuated TAA-induced hepatocarcinogenesis. In contrast, Cirp-deficiency showed only slightly attenuated liver tumorigenesis induced by a single diethylnitrosamine injection, whose tumorigenesis was associated with minimal chronic liver inflammation, injury, and fibrosis. The risk of human HCC recurrence is positively correlated with Cirp expression in liver. Cirp appears to play a critical carcinogenic function in chronic liver inflammation.

P01-3

Plectin Knock-Down Promotes Cell Migration of Human Liver Cells by Increased Rac1-GTPase Activity

Yi-Hsiang Liu¹, Chiung-Chi Cheng¹, Yen-Chang Clark Lai², Yih-Shyong Lai¹

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The cross-linking function of plectin is maintaining uniformity of cell size and shape. We had confirmed that plectin deficiency altered the organization of cytokeratin18 and underlies the pleomorphic transformation of human liver cells. In this study, we will explore whether plectin deficiency can increase the migration of liver cells. Plectin deficiency is triggered by RNA knock-down in Chang cell; after that, cell migration is measured and compared with mock cells. The expression of molecules involving cell migration is then observed by Western blot and immunofluorescence. From transwell migration assay, plectin siRNA knockdown cells showed a higher migration compared to mock cells. Moreover, plectin knockdown cells were less organized and more polarized. The plectin knockdown cells also showed a higher relative Rac1-GTPase activity by Rac1 pull down assay. Conclusively, plectin deficiency in human liver cell modulate higher cell motility and was related to Rac1-GTPase pathway.

P02-1

microRNA-21 Expression in Human Hepatocellular Carcinoma Tissues

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Aim: The aim of this study is to characterize cellular phenotype and localization of microRNA-21(miR-21)-positive tumor cells in HCC. **Design:** In situ hybridization for miR-21 and immunostain for HepPar 1, CK7, 8 hepatic stem/progenitor cell markers, and TGF- β 1 were performed on 52 HCC tissues. Relationship between miR-21 expression and clinicopathological features of HCC was evaluated. **Results:** miR-21-positive tumor cells were shown in 31 of 52 HCC cases. The presence of HBV infection, the amount of fibrous stroma and histological grade were significantly associated with miR-21 expression. Moreover, 16 of 31 miR-21-positive HCCs contained small tumor cell clusters with high expression of miR-21. The miR-21-positive small cell clusters were positive for more than 1 hepatic stem/progenitor cell markers in 13 of 16 HCCs. **Conclusion:** Small HCC cell clusters with high expression of miR-21 showed immunohistochemical phenotypes of intermediate cells, suggesting hepatic progenitor cell origin.

P02-2

Hepatocarcinogenesis by Aberrant Microrna Expression by After Finishing Chronic Hepatitis C by Interferon

Yoshiki Murakami¹, Akihiro Tamori¹, Shoji Kubo², Ritsuzou Kozuka¹, Hiroyuki Motoyama¹, Etsushi Kawamura¹, Atsushi Hagihara¹, Hideki Fujii¹, Shuji Iwai¹, Sawako Uchida-Kobayashi¹, Hiroyasu Morikawa¹, Masaru Enomoto¹, Toshihito Tanahashi³, Y-H Taguchi⁴, Norifumi Kawada¹

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Hepatocellular carcinoma (HCC) develops in 2.5–4.2% of patients after the successful treatment of chronic hepatitis C virus (HCV) infection using interferon therapy. The aim of this study was to characterize microRNA (miRNA) expression in liver tissues from patients who achieved a sustained viral response (SVR). Seventy-one HCC, 61 HCC from patients with infected HCV (HCV-HCC) and 10 from patients who had achieved SVR (SVR-HCC) were enrolled. The miRNA expression

patterns were analyzed using microarrays. We could discriminate between SVR-HCC and HCV-HCC with 75.36% accuracy using the expression pattern of six specific miRNAs. The expression levels of 37 miRNAs were significantly lower in HCV-HCC than in SVR-HCC, whereas the expression of 25 miRNAs was significantly higher in HCV-HCC than SVR-HCC ($P < 1.0E-05$). Comprehensive miRNA expression analyses could not only differentiate between SVR-HCC and HCV-HCC but also forecast hepatocarcinogenesis after achieving SVR.

P02-3

Comprehensive Serum Glycan Analysis in Patients with Hepatocellular Carcinoma

Kazuhiro Nouse¹, Koji Miyahara¹, Hideaki Kinugasa¹, Yuki Morimoto¹, Chihiro Dohi¹, Yasuto Takeuchi¹, Nozomu Wada¹, Kenji Kuwaki¹, Hideki Onishi¹, Fusao Ikeda¹, Yasuhiro Miyake¹, Shinichiro Nakamura¹, Hidenori Shiraha¹, Akinobu Takaki¹, Maho Amano², Shin-Ichiro Nishimura², Kazuhide Yamamoto¹

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Aim: To identify serum glycans differentially expressed in hepatocellular carcinoma (HCC) and to know their abilities for the clinical use. **Method:** Glycan expressions in the serum of 114 HCC and 107 chronic liver diseases (CLD) were analyzed by high-throughput comprehensive Sweet Blot. **Results:** Sixty one glycans were detected by the method. Fourteen out of the 61 glycans were differentially expressed between HCC and CLD. Eight glycans among 14 glycans were fucosylated. AUROC of the combination of 6 glycans that minimize akaike information criteria for the diagnosis of HCC was 0.95. Three and 8 glycans were closely correlated with lymphnode metastasis and extrahepatic metastasis, respectively. Most of the up-regulated glycans in HCC with the metastasis were highly branched glycans and a tetra-antennary glycan (m/z3560) showed the highest odds ratio (15.2) of the extrahepatic metastasis ($p = 0.001$). **Conclusion:** Serum glycans are useful clinical markers in patients with HCC.

P03-1

Identification of Transforming Hepatitis B Virus S Gene Nonsense Mutations in Hepatocellular Carcinoma

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Whether HBV play a direct role in hepatocarcinogenesis is still uncertain. 25 HBV-related HCC patients positive for hepatitis B core antigen (HBcAg) in the cancerous parts of their HCC liver tissues were significantly associated with cirrhosis and small tumor size (≤ 2 cm) when compared with HBcAg(-) HCC patients. Southern blot analyses revealed freely replicative forms of HBV in the cancerous parts of HBcAg(+) HCC. Three nonsense mutations of S gene (sL95*, sW182*, and sL216*) were identified in the HBcAg(+) HCC tumor tissues. Functional studies of the 3 mutants demonstrated higher cell proliferation and transformation abilities than wild type HBV S gene, especially sW182*. Tumorigenicity analysis by xenograft experiments and in vitro migration assay showed potent oncogenic activity of sW182* mutant. This study has demonstrated potent oncogenic activity of nonsense mutations of HBV S gene, suggesting they may play an important role in hepatocarcinogenesis.

P03-2

Host Immune System in Markers of Carcinogenesis and Response in Patients with Hepatocellular Carcinoma

Teppei Matsui, Hidenari Nagai, Yu Ogino, Daigo Matsui, Takanori Mukozu, Noritaka Wakui, Kouichi Momiyama, Mie Shinohara, Koji Ishii, Yoshinori Igarashi, Yasukiyo Sumino

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Background: It has been reported that Th2 cytokines down-regulate antitumor immunity, while Th1 cytokines up-regulate it. **Aim:** To clarify the effectiveness of host immunity in patients with HCV-related liver diseases. **Patients/Methods:** 72 patients with HCV-related liver diseases included 19 patients with chronic hepatitis (F1:10 and F2:9), 6 patients with liver cirrhosis (F4), 12 patients with

early hepatocellular carcinoma (eHCC), and 35 patients with advanced HCC (aHCC). The aHCC group received hepatic arterial infusion chemotherapy (HAIC). **Results:** Treg cells were significantly higher in patients with HCC than in those without cancer. In aHCC patients with PD, Th1 cells were significantly decreased after HAIC. Treg cells were significantly decreased after HAIC in patients with PR and SD, but were significantly increased in PD patients. **Conclusions:** These results suggest that evaluation of the Th1/Th2 balance and Treg provides markers of carcinogenesis and curative effect.

P03-3

Evaluation of Serum Advanced Glycation End Products in Non-B and Non-C Hepatocellular Carcinoma

Hiroshi Kan¹, Hiroshi Aikata¹, Hideyuki Hyogo¹, Sho-ichi Yamagishi², Masayoshi Takeuchi³, Hatsue Fujino¹, Tomoki Kobayashi¹, Takayuki Fukuhara¹, Yohji Honda¹, Noriaki Naeshiro¹, Tomokazu Kawaoka¹, Masataka Tsuge¹, Akira Hiramatsu¹, Michio Imamura¹, Yoshiiku Kawakami¹, Hidenori Ochi¹, Kazuaki Chayama¹

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In this study, we evaluated the clinical significance of advanced glycation end products (AGEs) in patients with non-B and non-C hepatocellular carcinoma (NBNC-HCC). Ninety NBNC-HCC, 56 NASH and 27 control subjects underwent clinical laboratory examination including AGEs. The serum levels of AGEs were found to be significantly higher in patients with NBNC-HCC compared with NASH and controls [9.1 ± 2.7 , 5.2 ± 1.7 , 3.5 ± 1.2 (U/mL), respectively, $p < 0.05$]. There was no significant difference between etiology groups (NASH; 9.1 ± 2.1 vs heavy alcohol consumption; 8.9 ± 1.8 vs cryptogenic; 10.1 ± 3.7). Univariate analysis showed that AGEs were associated with age, AST, GGT, HDL-C (inversely), fasting plasma glucose, and HbA1c. By the use of multiple stepwise regression analysis, age, GGT, and HDL-C remained significant and were independently related to AGEs. AGEs might be involved in the pathogenesis of NBNC-HCC, thereby being a biomarker that could discriminate NBNC-HCC from NASH.

P04-1

Usefulness of Hypersensitive Measurement of AFP L3 Fraction to Predict Hepatocellular Carcinoma

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Background and Aims: AFP and AFP L3 fraction values were recognized as a useful serum marker of hepatocellular carcinoma (HCC). However, the clinical significance of high AFP L3 fraction with normal AFP levels is remains to be elucidated. The aim of this study is to investigate the usefulness of AFP L3 fraction using hypersensitive AFP assay (μ TAS). **Methods:** Among 1489 people who measured the AFP during August and September in 2010, 64 patients who showed abnormal high AFP L3 fraction values ($\geq 10\%$) in spite of normal AFP values (< 10 ng/ml) were entered this study. **Results:** During follow-up periods, including first and recurrence, HCC were diagnosed in 35 patients (54.7%). The accumulation hepato-carcinogenesis rate was 17.2% (6 months), 25% (1 year), and 35.9% (2 years). **Conclusions:** Prospective study revealed that patients with normal AFP value and high AFP L3 fraction developed HCC to a high rate, and suggest that such patients are at high risk of HCC.

P04-2

DES- γ -Carboxy Prothrombin Measured by P-11 and P-16 Antibody Is a Novel Biomarker for Hepatocellular Carcinoma

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Des- γ -carboxy prothrombin (DCP) are used in the diagnosis of hepatocellular carcinoma (HCC). However, there is an aberrant increase in serum DCP. This study aimed to elucidate the utility of NX-PVKA for early diagnosis of HCC. A total of 88 patients were included in the HCC group. The control group included 121 liver cirrhosis (LC) patients without HCC. The NX-PVKA ratio was calculated by dividing DCP by NX-PVKA. In patients not taking warfarin, the AUC values of DCP, NX-PVKA ratio and AFP were 0.709, 0.680 and 0.725, respectively. In cases with DCP > 35 mAU/ml in particular, a significant increase in NX-PVKA ratio was observed in patients with HCC. In those cases, the cut-off value for NX-PVKA ratio that was optimized by the ROC curve was 1.15. In addition, the sensi-

tivity and specificity in diagnosing HCC were 64.6% and 81.9%, respectively. These results suggest that, when used in combination with DCP, NX-PVKA ratio is a promising novel marker for the detection of HCC.

P04-3

Half-Life of Tumor Markers After Hepatic Resection for Hepatocellular Carcinoma

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Background: We evaluated the impact of half-life (HL) in tumor markers for hepatectomized HCC. **Methods:** HL was calculated from preoperative and post-one-month value. We defined 3 categories: early complete remission (CR), shorted HL (Short), and prolonged HL (Long) if the HL exceeded median value (AFP-HL; 6.5 days, DCP-HL; 4.8 days). **Results:** [AFP-study] Five-year RFS and OS of CR (n = 21), Short (n = 65) and Long (n = 45) were 41.4%, 29.9% and 18.7% (CR vs Long, p = 0.04), and 79.4%, 66.8% and 41.7% (CR vs Long, p = 0.01), respectively. Long HL was one of independent prognostic factors for OS in multivariate analysis. [DCP-study] Five years RFS and OS of CR (n = 104), Short (n = 32) and Long (n = 29) were 26.9%, 6.1% and 0% (CR vs Long, p < 0.01) and 61.0%, 57.7% and 30.0% (CR vs Long, p = 0.02), respectively. Multivariate analysis revealed that Long HL was one of independent prognostic factors for RFS and OS. **Conclusion:** HL of AFP and DCP may be useful to predict prongnosis for HCC after hepatectomy.

P05-1

Direct Renin Inhibitor Suppressed the Hepatocarcinogenesis Along with Anti-angiogenesis in Rats

Yosuke Aihara, Hitoshi Yoshiji, Ryuichi Noguchi, Tadashi Namisaki, Kei Moriya, Mitsuteru Kitade, Akitoshi Douhara, Norihisa Nishimura, Kosuke Takeda, Hideto Kawaratani, Hiroshi Fukui

Third Department of Internal Medicine, Nara Medical University, Japan

We have reported that renin-angiotensin system (RAS) plays a pivotal role in hepatocarcinogenesis, and clinically used RAS inhibitory agents attenuated hepatocarcinogenesis by attenuating angiogenesis. The aim of our current study was to elucidate the effect of a recently developed direct renin

inhibitor (DRI), Aliskiren, in rat hepatocarcinogenesis model. Hepatocarcinogenesis was induced in male F344 rats by feeding choline-deficient L-amino acid-defined diet (CDAA) for 12 weeks. DRI treatment (50 mg/kg or 100 mg/kg) was performed along with CDAA diet. The number of hepatic pre-neoplastic lesions were markedly less after DRI treatment along with the suppression of neovascularization and hepatic VEGF expression in a dose-dependent manner. We also observed that DRI suppressed hepatic angiotensin-II production in the liver. Since DRI is widely used in clinical practice without serious side effects, DRI could represent a potential new strategy against hepatocarcinogenesis in the future.

P05-2

Soluble VEGF Receptor-2 May Be a Predictive Marker of Suppressive Effective of BCAA on the Cumulative Recurrence of HCC

Hitoshi Yoshiji, Ryuichi Noguchi, Tadashi Namisaki, Kei Moriya, Mitsuteru Kitade, Yosuke Aihara, Akitoshi Douhara, Norihisa Nishimura, Kosuke Takeda, Hideto Kawaratani, Hiroshi Fukui

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Biomarkers of anti-angiogenic therapy that could predict clinical benefit would be an important and imperative issue. The aim of the current study was to identify the non-invasive predictive biomarker of clinical beneficial effect with Branched-chain amino acid (BCAA) on the cumulative recurrence of HCC. BCAA granules (Livact; 12 g/day) were administered for 60 months following the local curative therapy for HCC, and several indices were elucidated. The treatment with BCAA markedly inhibited the cumulative recurrence of HCC with high insulin resistance (IR) index (homeostasis model assessment; HOMA-IR: >2.5), but not HOMA-IR of ≤ 2.5 . BCAA also improved the HOMA-IR. Serum level of soluble form of VEGF receptor-2 (sVEGFR2) was significantly inhibited along with these clinical effects. BCAA may represent a new strategy for secondary chemoprevention for the HCC patients with IR, and sVEGFR2 may be a useful clinical predictive marker for BCAA treatment under the IR condition.

P05-3

Does Inhibition of Renin Angiotensin System Affects Prognosis of Advanced Hepatocellular Carcinoma Receiving Sorafenib?

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Background: The renin angiotensin system (RAS) had been thought to have an active role in carcinogenesis and RAS inhibition associated tumor growth prevention was recently reported not only on hepatocellular carcinoma (HCC) but also pancreatic cancer. **Aim:** To evaluate an additional tumor preventive effect of RAS inhibitor for patients with advanced HCC who have been treated by an oral multikinase inhibitor “Sorafenib” which is efficacious for VEGF suppression. **Methods:** In the thirty-five HCC patients (male 27/female 8, median age 71 yrs.), progression free survival (PFS) and mean survival time (MST) were examined retrospectively according with or without patient’s RAS inhibitor intake. **Results:** Unexpectedly, no significant differences in both PFS and MST ($p = 0.95$) were seen between the two groups, with and without RAS inhibitor intake. **Conclusion:** In this study, additional HCC prevention effect of RAS inhibitor through anti-VEGF signaling, was not well displayed probably because of powerful VEGF suppression by sorafenib.

P06-1

Clinical Features of Early Cancers

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In 2009, international consensus of early liver cancer defined as hepatocellular nodule having vaguely border & stromal invasion without vascularization. However we don’t know the clinical features of early cancer exactly. Method; Since 2000, we have followed 910 patients with chronic liver disease & detected. 169 small HCCs (less than 2 cm) & examined add small HCCs by angio-CT system. Result; Only 13 small liver cancers were early cancers. 3 were resected & 1 was treated by RFA after biopsy & others were observed until changed to typical cancers. There early cancers changed to typical cancers often 0.8–6.5 over years. During follow-up

early cancer did not metastasize & grew up very slowly. Conclusion; Early cancer was fewer than expected & had not cancer characters.

P06-2

Significance of Preoperative EOB-MRI and Simultaneous Treatment of Early HCC at Hepatic Resection of Progressed HCC

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Purpose: The purpose was to clarify whether preoperative EOB-MRI and simultaneous treatment of early HCC (eHCC) at the time of hepatic resection (Hx) for progressed HCC affected patient prognosis following Hx. **Methods:** 77 patients underwent EOB-MRI (EOB(+)) and 70 patients did not (EOB(-)). Suspected eHCCs were resected or ablated at the time of Hx for progressed HCC. **Results:** The number of patients who underwent treatment for eHCCs was significantly higher in the EOB(+). Recurrence-free (RF) survival (1-, 3-, and 5-year; 81.4, 62.6, 48.7% versus 82.1, 41.5, 25.5%, respectively, $p < 0.01$), but not overall survival (1-, 3-, and 5-year; 98.7, 90.7, 80.8% versus 97.0, 86.3, 72.4%, respectively, $p = 0.38$) was significantly better in the EOB(+). Univariate and multivariate analyses showed that EOB-MRI was one of the independent factors significantly correlated with better RF survival. **Conclusions:** Preoperative EOB-MRI and simultaneous treatment of eHCC prolonged RF survival after Hx.

P06-3

Risk Factors for Early Recurrence After Curative Hepatic Resection for Small and Solitary Hepatocellular Carcinoma

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Aim: To clarify risk factors for early recurrence after curative resection for small, solitary hepatocellular carcinoma (HCC). **Methods:** The consecutive 67 patients who underwent curative hepatectomy for small solitary HCC (<3 cm) accompanied with chronic hepatitis or Child A cirrhosis were enrolled in this retrospective cohort study. Between 19 patients suffering from recurrence within 2 years of surgery and the remaining 48 patients, risk factors for early recurrence after liver resection were analyzed by multivariate analyses. **Results:** Two-year recurrence rate for the all patients was 28.4%. Multivariate analysis showed that non-simple nodular type as the gross tumor classification (OR5.6, 95% CI 1.2–27, $p = 0.032$) and microvascular invasion (OR8.0, 95% CI 1.3–51, $p = 0.028$) were independent and significant risk factors for early recurrence. **Conclusions:** The gross tumor classification and microvascular invasion had impact on early recurrence after hepatectomy for the small, solitary HCC.

P07-1

A Liver Fibrosis Marker, FIB-4 Index, As a Biomarker for Long-Term Outcomes of HCC Patients After Curative Resection

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Objectives: Liver fibrosis is a risk factor for HCC. FIB-4 index is a laboratory marker that reportedly correlated with the degree of liver fibrosis. We investigated the effect of FIB-4 index on the recurrence and survival in HCC patients who underwent curative hepatectomy. **Methods:** A total of 431 consecutive patients who underwent hepatectomy for primary HCC were analyzed. FIB-4 index was calculated at the time of HCC diagnosis. Postoperative recurrence and survival rates were compared according to tumor characteristics,

tumor markers, and FIB-4 index. **Results:** Pretreatment FIB-4 index was associated with recurrence and survival rates, independent of HCC progression or tumor marker levels in multivariate analysis. Recurrence rates were higher in and survival rates were lower after hepatectomy patients with FIB-4 index >3.25 versus <3.25 ($P = 0.0049$ and 0.0030). **Conclusions:** FIB-4 index is a predictor for the outcomes in patients with HCC treated with curative hepatic resection.

P07-2

Estimation of Hepatocellular Carcinoma for Patients with HBV Infection by HBS Antigen and FIB-4 Index

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Aim: FIB-4 index is a fibrosis marker and HBs antigen reflects the degree of intrahepatic replication of HBV. We estimated the incidence of HCC by the combination of these two parameters. **Methods:** 677 HBsAg-positive cases were classified into three groups: 203 HBeAg-positive cases (G-I), 366 HBeAg-negative cases with ALT elevation (G-II) and 108 HBeAg-negative with persistently normal ALT for >3 years (G-III). **Results:** Mean value of FIB-4 and $\log_{10}$ HBsAg for each group was 2.36, 2.91, 2.07 and 3.62, 3.04, 2.45. HCC occurrence rate for low FIB-4 (<1.0), moderate FIB-4 (1.0–2.0) and high FIB-4 (>2.0) was 1.7, 11.5, 35.6%. HCC occurrence rate for low HBsAg ($\log_{10}$ HBsAg <2.0), moderate HBsAg (2.0–3.0) and high HBsAg (>3.0) was 31.7, 26.6, 16.2%. For cases with FIB-4 >2.0 and $\log_{10}$ HBsAg <2.0, HCC incidence was 80.0, 45.5, 37.9% for each group. **Conclusions:** Combined analysis with FIB-4 and HBsAg showed usefulness for estimating HCC occurrence.

P07-3

Value of Shear Wave Velocity Measurements for the Risk Assessment of HCC Development in Patients with NAFLD

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Purpose: To evaluate the value of measuring shear wave velocity (VTTQ) for the risk assessment of HCC development. **Methods:** VTTQ was measured twelve times in the liver of 163 NAFLD patients including 14 HCC cases. **Results:** VTTQ was 3.04 ± 0.17 m/s and 1.27 ± 0.25 m/s in patients with and without HCC, respectively, and was significantly higher in HCC cases ($p < 0.001$). The robust coefficient-of-variation was significantly higher in the left than in the right ($p = 0.018$) and significantly increased as VTTQ increased ($p = 0.0002$). Multivariate analysis showed that VTTQ ($p = 0.006$) was the independent explanatory factor for HCC presence. The AUROC in the differentiation of HCC from non-HCC was 0.943 for VTTQ and was comparable with that for other noninvasive markers such as BARD (0.838). **Conclusions:** These results suggest that fibrosis occurs heterogeneously throughout the liver and that VTTQ measurements are useful in HCC risk evaluation in a NAFLD cohort.

P08-1

Fusion Imaging and Contrast Enhanced US Guidance in RFA Therapy for HCC Poorly Defined with B-Mode US

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Aim: This study investigated the effectiveness of fusion imaging and CEUS guidance in ablation for HCC. **Materials and Methods:** Between January 2007 and October 2013, forty patients (22 men, 18 women) with 65 hypervascular HCCs were enrolled. HCCs were treated by RFA under fusion imaging and CEUS using perfluorocarbon microbubbles guidance in RFA for target lesions that could not be visualized clearly by B-mode US. **Results:** The maximal diameters of all tumors ranged from 0.7 to 2.3 cm (mean $\pm$ SD, $1.3 \text{ cm} \pm 0.6$) on US. Complete tumor necrosis was achieved by a single session of RF ablation in 36 (90%) of the 40 patients, while two

sessions were required for the remaining four (10%) patients. The average number of treatment sessions was 1.1. As the control, the average numbers of treatment sessions of fusion imaging alone guidance or CEUS alone guidance were 1.09 and 1.09, respectively. **Conclusion:** Fusion imaging and CEUS-guided RFA is an efficient approach for HCCs.

P08-2

Virtual Ultrasonography Constructed by Gd-EOB-DTPA-Enhanced MRI is Useful to Avoid the Bile Duct Injury by RFA

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Background/Aims: The aim of this study is to prospectively evaluate the contribution for safety and utility of radio-frequency ablation (RFA) assisted by this virtual technology.

Methods: Bile duct anatomy was assessed in 203 patients who underwent Gd-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) for the evaluation of hepatic tumor. Eighty-one of these patients subsequently underwent RFA assisted by ultrasound imaging. **Results:** Virtual ultrasonography was able to visualize the common bile duct, left hepatic duct, and right hepatic duct. The target hepatic tumor nodule and biliary duct could be detected with virtual ultrasonography in all patients, and no severe complications occurred. **Conclusions:** The running pattern of the bile ducts could be recognized on conventional ultrasound by referencing virtual ultrasonography. This imaging technology is useful to avoid the bile duct injury, which was induced by RFA.

P08-3

Usefulness and Limitations of the VirtuTRAX Instrument Navigator in Assisting RFA

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Background: The VirtuTRAX Instrument Navigator is an exciting new advancement, which uses electromagnetic technology to visually track the instrument tip in real time. This intuitive device is compatible with imaging systems using navigation technology and allows physicians to accurately track the tip of an RFA probe. In this, we evaluated the usefulness and limitations of the VirtuTRAX system in assisting RFA. **Method:** 36 patients were treated by RFA performed using VirtuTRAX at our center. RFA was performed with the GE Logiq E9 system by using a C1-5 probe. **Results:** The VirtuTRAX allowed the needle tip to be precisely detected during the ablation, enhancing patient safety in all cases. Most patients could be easily treated using the system. However, there were also some problems, such as set up time and the positional gap caused by the deflection of the needle. **Conclusions:** By providing virtual puncture needle navigation, the VirtuTRAX system easily shows the needle tip.

P09-1

Tracking Navigation Imaging of TACE for HCC Using Cone-Beam CT Angiography

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Purpose: To evaluate, using a new tracking navigation imaging software program, the usefulness of 3D CT angiography for transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). **Methods:** Fifty-two patients with 73 HCCs were enrolled retrospectively. Arteries feeding the tumor were traced automatically

by adjusting the region of interest around the targeted tumor on axial and coronal images using the tracking navigation imaging with 3D cone-beam CT angiography. **Results:** Using final selective angiographic findings as the gold standard, the detection of feeding vessels was 90.4% (66/73) for the tracking navigation imaging and 50.7% (37/73) for celiac trunk angiography ($p < 0.001$). The sensitivity and specificity for the detection of feeding arteries were 97.1% (66/68) and 80.0% (4/5), respectively. **Conclusion:** Tracking navigation imaging should be useful for TACE in HCC patients with complicated feeding arteries.

P09-2

Early Response Prediction of Hepatocellular Carcinoma to Transcatheter Therapies Using Intraprocedural Plain Cone-Beam CT

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Aim: The purpose of this study was to assess the usefulness of intraprocedural plain cone-beam CT for early response prediction of conventional TACE/TAI for HCC. **Material and Methods:** Between April 2011 and April 2012, we studied eighty-nine patients (53 men, 36 women; mean age, 72.7 years) with 166 hypervascular HCCs. The primary objective was to evaluate the diagnostic performance of intraprocedural plain cone-beam CT compared with 1–2 months CT follow-up for assessing treatment response. **Results:** At 1–2 months CT follow-up, complete, partial tumor response or progressive disease was seen in 96 HCCs, 52 HCCs and 18 HCCs, respectively. According to ROC curve analyses for distinguishing recurrent tumor from treatment effect, the cutoff of mean voxel value on intraprocedural plain cone-beam CT was 206 (AUC, 0.809). **Conclusion:** Poor iodized oil accumulation on plain cone-beam CT was an unfavorable predictor in HCC patients treated with TACE/TAI.

P09-3

Clinical Trial of F-18 Fluoroacetate PET/CT in Liver Tumors

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Background & Aims: F-18 Fluoroacetate (FACE) is a F-18 fluorinated acetate, which is known to be metabolically trapped in TCA cycle and is expected to be a promising oncologic PET tracer. The aim of this study was to evaluate the usefulness of FACE as an oncologic PET tracer in the diagnosis of liver tumors. **Methods:** Ten patients with liver tumors (5 hepatocellular carcinomas, 1 cholangiocellular carcinoma, 4 metastatic liver tumors) were evaluated by PET/CT using SUVmax and TNR (Tumor-to-normal Liver Ratio). **Results:** F-18 Fluorodeoxyglucose (FDG) was positive in 4 tumors and negative in the other 6 tumors, while FACE was also positive in 4 tumors, which were the same tumors with positive FDG uptake. FDG uptake of liver tumors (SUVmax: 6.5 ± 4.2 , TNR: 2.6 ± 1.7) was significantly higher than that of FACE (2.7 ± 0.6 , 1.5 ± 0.4). **Conclusion:** Tumor FACE uptake was confirmed, though the features of F-18 FACE were not observed. Further studies are needed.

P10-1

Imaging of Focal Nodular Hyperplastic-Like Nodules in Alcoholic Liver Cirrhosis Using Gd-EOB-DTPA MRI

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Focal nodular hyperplastic (FNH)-like nodules arising in patients with alcoholic liver cirrhosis could not be easily differentiated from well-differentiated HCCs. Few reports have examined the EOB MRI imaging findings of FNH-like nodules arising in patients with alcoholic liver cirrhosis (LC). Three patients with a history of alcohol abuse who presented with multiple hepatic nodules are herein examined. Dynamic computed tomography revealed multiple nodular lesions, which were enhanced at the early contrast phase. In the hepatobiliary phase using EOB MRI, these tumors did not show uptake, suggesting the presence of HCC. Ultrasound guided biopsy revealed a slight increase in cell density, sinusoidal

dilatation, and contained unpaired small arteries. From these findings, the nodules were diagnosed as FNH-like nodules arising in alcoholic-cirrhotic livers. The differential diagnosis of FNH-like nodules and HCC is difficult with EOB MRI; thus, histological confirmation is necessary.

P10-2

Morphometric and Immunohistochemical Study of Cholangiolocellular Carcinoma: Comparison with Non-Neoplastic Bile Duct

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Background/Purpose: The origin of cholangiocellular carcinoma (CoCC) is still controversial. **Material and Methods:** Cancerous ducts: Fifteen CoCC lesions from 15 cases. Non-neoplastic ducts: Twenty specimens of non-cancerous areas of 20 liver cancer cases. From these specimens, cholangioles, interlobular ducts of small size (ILD-S), interlobular ducts of medium size (ILD-M) and septal ducts were randomly selected. Morphometry: The outer and inner diameters of these ducts were measured. Immunohistochemistry: Two hepatocyte markers (Hep Par 1 and α -fetoprotein (AFP)), 2 cholangiocyte markers (cytokeratin CK7, CK19), a marker for mucin (Muc1), a hepatic stem/progenitor cell marker (c-Kit) and epithelial membrane antigen (EMA) were used. **Results:** Morphometry: CoCC ducts morphologically resembled ILD than cholangiole. Immunohistochemistry: Character of CoCC resembled ILD than cholangiole. **Conclusion:** These results suggest that CoCCs may originate from ILDs.

P11-1

Breast Cancer Resistance Protein (BCRP) Expression Predicts Outcome of Patients with Hepatocellular Carcinoma

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Aims: The correlation between chemoresistance caused by imbalance of drug influx and efflux and outcome of patients with hepatocellular carcinoma (HCC) still remains unclarified. We aimed to examine whether the expression of uptake trans-

porters, organic cation transporter 1 and 3 (OCT1 and OCT3) as well as efflux transporters, breast cancer resistance protein (BCRP), multidrug resistance protein1 (MDR1) and MDR associated protein2 (MRP2) become predictive factors in HCC. **Methods:** Immunohistochemical analysis of the transporter proteins has been performed with HCC samples (n = 24) in relation to clinical data. **Results:** OCT1 and OCT3 expression were markedly lower in HCC than in adjacent non tumor tissue (NT). BCRP expression was marginally higher in HCC than in NT. Kaplan Meier analysis revealed that high BCRP expression significantly related to improved survival and prolonged time to relapse in patients with HCC. **Conclusions:** BCRP may serve as a potential prognostic and therapeutic marker for HCC.

P11-2

Liver Factors in Relation to HCC Aggressiveness Phenotype

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Background: Liver damage predisposes to HCC and inflammation is a prognostic factor. **Aim:** To evaluate liver factors in relation to tumor characteristics. **Methods:** A 4000 Taiwan HCC patient database was examined. HCC parameters in low and high bilirubin patients were compared. **Results:** Patients were dichotomized by bilirubin > or <1.5 mg/dl. For <3 cm HCCs, significant differences for > high bilirubin patients were: less Child A (26 vs 88%) and more Child B (53 vs 11%) cirrhosis, similar tumor size (mean 2.1 cm) and AFP levels, significantly more tumor multifocality (20 vs 12%) and PVT (11 vs 1.8%). HCC >3 cm size patients had parallel differences, but also significantly higher mean tumor size (9.0 vs 6.7 cm) and AFP levels (765 vs 71) in the high bilirubin patients. **Conclusions:** Abnormal liver function in HCC patients is associated with a more aggressive tumor phenotype. This cannot be explained by parenchymal liver destruction, at least for the small tumor size patients.

P11-3

Clinicopathological Features and Surgical Outcomes of NAFLD-HCC

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Introduction: There is uncertainty about the characteristics and prognosis of nonalcoholic fatty liver disease-associated hepatocellular carcinoma (NAFLD-HCC). **Objective:** We evaluated the clinical and pathological features of surgically treated NAFLD-HCC as well as surgical outcomes and factors related to recurrence/death. **Methods:** We retrospectively enrolled 26 postoperative HCC cases between 1998–2012 that fulfilled the criteria of: 1) fatty deposition >10% in background tissue; 2) alcohol uptake <22 g/day; 3) negative for HBsAg, HBcAb, HBsAb, and HCVAb; and 4) exclusion of autoimmune hepatitis, primary biliary cirrhosis, and citrullinemia cases. **Results:** The median observation period was 5.1 years in our predominantly male (92%) cohort. Median age (71 years) and BMI (25.2 kg/m²) were both relatively high. Diabetes mellitus (DM), hypertension (HT), and hyperlipidemia were present in 81/58/27% of cases, respectively. Median of preoperative data were as follows: platelet count, 16×10⁴/μl; prothrombin time, 99%; albumin, 4 g/dl; alanine aminotransferase, 37 IU/l; gamma-glutamyl transpeptidase, 88 IU/l; HOMA-IR, 5.4; HbA1c, 6.5%; total cholesterol, 186 mg/dl; ferritin, 184 ng/ml; alpha-fetoprotein, 12 ng/ml; DCP, 92 mAU/ml; ICGR-15, 12%; and Child-Pugh score, 5. HCC stages as defined by the Liver Cancer Study Group of Japan of I/II/III/IV were 4/65/31/0%, respectively. HCC tumor size was 4 cm, and 31% of cases had multiple HCCs. Patients positive for tumor capsule/capsule invasion/vascular invasion/intrahepatic metastasis were 59/31/15/4%, respectively. Tumor differentiation sorted as well/moderate/poor was 23/69/8%. With regard to operative procedure, partial/sub-segmental/segmental/lobe resection was 38/31/23/8%. In the background liver, NAFLD activity scores (NAS) of 1/2/3/4/5/6/7–8 were 4/38/19/23/12/4/0% and fibrosis scores of F0–2/3/4 were 31/38/31%. The 3/5/10-year postoperative recurrence rates were 0.55/0.55/0.68. Kaplan-Meier/Log-rank testing indicated that multiple HCCs (P = 0.02), HCC size >5 cm (P < 0.001), HCC stage (P = 0.003), operative procedure (P = 0.02), and tumor differentiation (P = 0.04) were significantly higher in recurring HCC cases. Postoperative 3/5/10-year mortality rates were 0.86/0.75/0.66, respectively. Kaplan-Meier/Log-rank testing showed that HT (P = 0.03) was significantly higher in fatal HCC cases. **Conclusions:** In our cohort, surgically treated NAFLD-HCC patients were mainly male with obesity/DM/HT. Patients often had carcinogenesis despite low NAS/fibrosis in background tissue.

Multiple HCCs, HCC size > 5 cm, HCC stage, operative procedure, and tumor differentiation/HT are thought to be factors related to recurrence/death in postoperative NAFLD-HCC cases.

P12-1

PTAT vs SR in the Treatment for Early-Stage HCC in China: A Meta-Analysis of Randomized Controlled Trials

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Aim: To compare the efficacy of percutaneous thermal ablation therapy (PTAT) and surgical resection (SR) for early-stage hepatocellular carcinoma (eHCC). **Methods:** Relevant randomized controlled trials (RCTs) in China were gathered until October 2013 to identify studies assessing clinical efficacy. **Results:** Total of 776 eHCC patients in five RCTs, 368 were distributed to PTAT group and 408 to SR group. there were no difference in the 1-, 2-, 3-yr overall survival (OS) between two groups, but SR was associated with higher 5-yr OS than PTAT. Additionally, the 2-, 3-, and 5-yr recurrence-free survival rates were significantly higher in SR group than that in PTAT group. SR was associated with higher incidence of complications and longer hospital duration than PTAT. **Conclusions:** SR could significantly improve 5-yr OS for eHCC patients, and reduce the postoperative recurrence. But from the view of minimally invasive, eHCC patient with severe liver cirrhosis is more suitable for PTAT.

P12-2

Endoscopic versus Open Hepatic Resection for Hepatocellular Carcinoma: A Propensity Matched Analysis

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Introduction: The aim of this study is to compare the efficacies of endoscopic hepatectomy (EH) and open hepatectomy (OH) for hepatocellular carcinoma (HCC) patients. **Methods:** From 1999, a total of 269 HCC patients who met the Milan criteria were enrolled. A one-to-one propensity matched analysis. **Results:** With propensity matching, 59 EH and 59 OH patients showed equivalent preoperative clinical characteristics. The median operative time and median blood loss were

significantly lower, and the median postoperative hospital stay was significantly shorter in the EH group). The cumulative 5- and 10-year disease-free survival rates were 35.2% and 15.6% in the EH, and 34.9% and 14.6% in the OH. The cumulative 5- and 10-year overall survival rates were 74.3% and 44.4% in the EH, and 67.6% and 60.8% in the OH. **Conclusions:** For HCC patients meeting the Milan criteria, EH is a safe and less invasive treatment modality with equivalent disease-free and overall survival when compared to OH.

P12-3

Outcome of the Liver Resection, Liver Transplantation, Local Therapy for HCC Less Than 3 cm, 3 Nodules

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Introduction: The aim of this study was to compare the outcome between local treatment, liver resection (LR) and living donor liver transplantation (LDLT) for HCC within Milan Criteria. **Methods:** We analysed the outcome in patients with HCC less than 3 cm and 3 nodules in comparison with local treatment of RFA, PEI and TACE, and LR and LDLT. **Results:** One hundred fifty patients with local treatment (72 RFA, PEI 23, TACE 67), 84 LR and 46 LDLT were enrolled. The 1-, 3-, 5-years survival rate were 96.3/85.9/70.1% in local treatment, 95.3/83.0/71.8% in LR and 80.9/73.3/67.7% in LDLT respectively (N.S.). The 1-, 3-, 5-years recurrence rate were 24.9/61.9/74.4% in local treatment, 20.6/43.5/60.6% in LR and 0/2.7/2.7% in LDLT ($p < 0.001$). The 1-, 3-, 5-years cancer related survival rate were 96.3/87.5/71.4% in local treatment, 97.6/89.9/80.7% in LR and 100/97.2/97.2% in LDLT ($p = 0.004$). **Conclusion:** LDLT was better recurrence rate and cancer related survival than local treatment and LR.

P13-1

Surgical Resection for Advanced Hepatocellular Carcinoma with Tumor Thrombi in the Inferior Vena Cava

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Background: Advances in surgical techniques have made a curative surgical approach to tumors involving both liver and inferior vena cava (IVC). The present study aimed to evaluate outcome of aggressive surgical management for HCC with tumor thrombi in IVC. **Methods:** We retrospectively reviewed the 21 cases HCC with IVC tumor thrombus (Vv3) who underwent hepatic resection in our hospital. **Results:** It was possible to perform the hepatic resection and the removal of tumor thrombus safely in all cases with no surgery-related death; no use of artificial cardiopulmonary bypass in 20 cases but one exception with self-pericardium in IVC reconstruction. The median operative time was 490 minutes (230–950); the median blood loss was 3950 ml (530–46,000). The surgical outcome of these cases in 1- and 2-year survival rates were 56.7% and 31.5%, respectively. **Conclusion:** Surgical resection for the advanced HCC with IVC tumor thrombus is the possible procedure with considerable oncological results.

P13-2

Over 40% Decrease in Platelet Count After Hepatectomy is Related with Liver Injury and Delayed Liver Function Recovery

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Background: Surgeons experience decrease in platelet count after hepatectomy. We assessed if this decrease is related with liver injury and delayed liver function recovery. **Methods:** In 220 patients who underwent hepatectomy, we classified patients with postoperative platelet count less than 60% of the preoperative as low group, and more than 61% as high group. We compared postoperative liver injury and delay in liver function recovery. Delayed postoperative recovery was defined as taking more than 7 days for PT to return to 80% of the preoperative. **Results:** Patients in low group had

lower PT, higher AST, ALT, and T-bil, and lower Alb than high group. Less than 60% of platelet count was identified as an independent risk factor for delayed liver function recovery.

Conclusions: Over 40% decrease in platelet counts was related with liver injury and delayed liver function recovery. These findings are in accordance with the evidence that platelets play pivotal roles in liver regeneration.

P13-3

Surgical Outcomes of Hepatocellular Carcinoma with Major Bile Duct Invasion

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Aim: The aim of this study was to clarify the surgical outcomes of hepatocellular carcinoma (HCC) with major bile duct invasion (MBI). **Methods:** We enrolled 43 patients who underwent hepatectomy for HCC with MBI, defined as invasion of the first branches of the bile duct or more. Overall survival, recurrence, and survival after recurrence were analyzed. **Results:** The 5-year survival rate was 33.1%. Child-Pugh B (HR, 4.06; 95% CI, 1.58–9.76) and major vascular invasion (MVI; HR, 2.63; 95% CI, 1.06–6.55) were independent prognostic factors for overall survival. Among the 40 patients who underwent macroscopic curative resection, the 5-year recurrence rate was 85.4%. MVI was the only independent prognostic factor for recurrence (HR, 3.17; 95% CI, 1.45–6.93). Survival after recurrence also differed significantly between patients with and without MVI (3-year survival rate, 11.9% vs. 46.2%; $P = 0.013$). **Conclusions:** MVI was a strong poor prognostic factor in the setting of HCC with MBI.

P14-1

Clinical Utility of Endovascular Treatment with Drug-Eluting Beads for Advanced Hepatocellular Carcinoma

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This study aims to assess the efficacy and tolerability of drug-eluting beads-transarterial chemoembolization (DEB-

TACE) in the treatment of hepatocellular carcinoma (HCC) in patients who were difficult to receive conventional TACE because of high ages or previous incomplete responses. We enrolled 5 patients (4 of men and one of woman with a mean age of 70) with uni- or multifocal HCC who underwent a DEB-TACE and evaluated overall target response and side effect. All patients showed child-pugh A stage of liver cirrhosis and no portal tumor thrombosis. All patients were successfully treated with DEB-TACE. No patients demonstrated no major side effects, however some patients showed low-grade fever and minimal abdominal symptoms. Our experience indicated that DEB-TACE may be a possible safe and effective in elderly patients with advanced HCC.

P14-2

Prognosis Scoring System for Receiving TACE in Patients with Intermediate-Stage HCC

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Background: The prognosis for patients with intermediate-stage hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) is variable. **Methods:** We included 350 patients with intermediate-stage HCC undergoing TACE at Chiba University Hospital (training cohort, $n = 187$) and two affiliation hospitals (validation cohort, $n = 163$). We performed Cox regression analysis of the prognostic factors and developed a point score. **Results:** The number of tumors (1 vs. 2–7 vs. 8 or more lesions), and the Child-Pugh score (5 vs. 6 vs. 7 vs. 8 or more) remained independent prognostic factors. These were used to generate the score that differentiated five groups (0–1, 2, 3, 4 and 5 or more points), and the median survival times were 67.1, 38.5, 24.1, 14.1 and 10.3 months, respectively ($p < 0.001$). These results were confirmed in validation cohort. **Conclusions:** The scoring system predicts the outcome in patients with intermediate-stage HCC undergoing TACE.

P14-3

The Effectiveness of Angiographic Subsegmentectomy as a Treatment Method Using the Hemodynamics of HCC

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Aim: We have performed Angiographic subsegmentectomy (AS) as a treatment method for patients with hepatocellular carcinomas (HCC) since 1998. Excellent outcomes of AS was already published on Cancer 2010. In this time we reported the further investment of AS. **Method:** The emulsion of iodized oil (Lipiodol) & anti-cancer drugs given from peripheral feeding artery flew into portal veins via drainage vessels & peripheral feeding artery was embolyzed by small particles of gelatin sponge. Resulted simultaneous embolization of peripheral portal veins & peripheral feeding artery occurred. This treatment method was named as Angiographic subsegmentectomy by late Prof. Okuda. **Result:** In 5 year survival rates of these 225 patients were 48.67% respectively (65.28% in stage I, 56.70% in stage II). 10 year survival rates were 22.70% respectively (36.81% in stage I, 19.23% in stage II). **Conclusion:** AS is one of the most effective treatment method of HCC.

P15-1

Sorafenib Might Improve Liver Fibrosis in Patients with Cirrhosis and Advanced Hepatocellular Carcinoma

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Aim: To clarify the effects of sorafenib (SF) on hepatic function and liver fibrosis (LF) in patients with liver cirrhosis (LC) and advanced HCC (aHCC). **Patients/Methods:** Sixty-two patients with LC and aHCC were treated with SF for 4 weeks. LF was assessed by virtual touch tissue quantification (VTTQ). **Results:** Assessment of liver damage showed that serum Alb was significantly lower after treatment compared with before treatment, although there were no significant differences of serum total T-Bil and % PT after treatment. These changes led to an increase of the Child-Pugh score. Assessment of LF

showed that serum type IV collagen decreased significantly after treatment compared with before treatment, but there was no significant change of serum hyaluronic acid after treatment. The medium VTTQ value also decreased significantly. **Conclusions:** In patients with LC and aHCC, SF might improve LF, but it might also exacerbate liver damage as indicated by a decrease serum Alb.

P15-2

Sorafenib Deteriorate Liver Function in Advanced HCC Patients: A Multi-Center Retrospective Study in Japan

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Background: Sorafenib has been approved for patients with advanced HCC in Japan since 2009. In this study, we retrospectively evaluated the influence of sorafenib on the liver function of patients. **Material and Methods:** We enrolled patients who received oral administration of sorafenib in 21 hospitals from 2009 to 2011 in Japan. **Results:** 388 patients received sorafenib monotherapy. Prognosis of patients who had deteriorated liver function during sorafenib therapy was significantly poor. In the 67 patients who obtained the disease control, cases who had deteriorated liver function during the treatment had significantly poor prognosis. Moreover, patients with mild ascites and albumin level less than 3.9 g/dL before treatment had poor prognosis. **Conclusions:** Sorafenib therapy deteriorated liver function irrespective of disease control in HCC patients. Liver function should be carefully monitored especially in patients with mild ascites or low albumin level during the sorafenib therapy.

P15-3

Branched-Chain Amino Acids Prolong Survival of Patients Treated with Sorafenib for Advanced Hepatocellular Carcinoma

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A multicenter retrospective analysis was performed to examine the antitumor efficacy of branched-chain amino acids (BCAA) granules combined with sorafenib therapy in advanced HCC patients. Two hundred seventy patients (84/16% Child-Pugh A/B) with advanced HCC were received sorafenib therapy between Jan 2009 and Dec 2012. Fifty six patients were treated with BCAA granules (group A) during the whole period of sorafenib therapy, and 214 patients were not (group B). In the Child-Pugh A cases, the median OS of group A (440 days) had a significantly better prognosis than group B (307 days) ($p < 0.05$). In the Child-Pugh A cases, both AFP < 100 ng/ml and the combined use of BCAA contributed to OS in the multivariate analysis. In the propensity score analysis which adjusted the confounding factors, the combined use of BCAA significantly contributed to OS ($p < 0.05$). The combined use of BCAA granules might improve OS in Child-Pugh A patients who were received sorafenib therapy against advanced HCC.

P16-1

Combination of Sorafenib and Hepatic Arterial Infusion Chemotherapy for Advanced HCC with Portal Venous Invasion

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Aim: To clarify the usefulness of combined treatment with sorafenib (SF) and hepatic arterial infusion chemotherapy (HAIC) for liver cirrhosis (LC) patients with advanced HCC (aHCC) and portal venous invasion (PVI). **Patients/Methods:** Forty-three adult Japanese LC patients with aHCC and PVI ($>Vp3$) were admitted to our hospital. Nineteen patients were treated with HAIC alone (H) and 7 patients were treated with HAIC + radiation therapy (H+RT), while 17 patients were treated with HAIC after receiving SF (SF+H). **Results:** The median survival time of the SF+H was significantly better than that of the H, while there was no significant difference between the H+RT and the H. After 4 weeks of treatment, a partial response (PR) was achieved in 15.8% of the H and 14.3% of the H+RT. The PR rate increased to 47.1% in the SF+H. **Conclusions:** When multimodal therapy is performed for LC patients with aHCC and PVI, performing HAIC after SF treatment might improve both the response and survival.

P16-2

Sorafenib Combined with TACE for HCC: Early and Severe Adverse Events are Associated with Better Survival

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Background and Aims: To examine sorafenib-related adverse events (AEs) and their relationship to survival in patients with unresectable hepatocellular carcinoma (HCC) receiving sorafenib combined with transarterial chemoembolization (TACE). **Methods:** we prospectively collected data from 142 consecutive HCC patients who received combination therapy with sorafenib and TACE. **Results:** During a median follow up of 7.9 months (interquartile range, . The presence of sorafenib-related AEs was an independent predictor of overall survival (hazard ratio: 0.465; 95% confidence interval: 0.261–0.829). The survival benefit was more significant if rash and

HFSR occurred within 4 weeks of starting treatment or if the severity of these AEs was increased. **Conclusions:** Sorafenib-related AEs can predict survival, especially early and severe dermatologic side effects in unresectable HCC patients treated with sorafenib plus TACE.

P16-3

Sorafenib and Surgical Treatment for Advanced Hepatocellular Carcinoma

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Aim: To clarify the efficacy of sorafenib. **Method:** Thirty-one HCC patients were treated with sorafenib (Child-Pugh A 24, B 7 and Stage III 3, IV-A 6, IV-B 23). **Result:** 1. One, 2 and 3-year OS were 62.9%, 49.5% and 35.4%, respectively and median survival time was 21.8 months after sorafenib administration. 2. Five patients who survived more than 3 years and all of them underwent surgical treatments; 4 hepatectomies and one open RFA. 3. The OS of the 5 patients was significantly better than that of the other patients (100% of 3-year OS and 29.1% of 2-year OS, $P < 0.005$). 4. Two patients survived without recurrences more than 3 years; one is huge HCC with portal invasion and multiple lung metastases and the other is unresectable hepatocellular carcinoma with inferior vena cava tumor thrombi (Vv3). Chemoembolization, radiotherapy, RFA or hepatectomy were additionally performed. **Conclusion:** Even for advanced HCC, sorafenib with adequate surgical managements can result in long-term survival.

P17-1

The Efficacy and Safety of Hepatic Arterial Infusion Chemotherapy Using System I for Advanced Hepatocellular Carcinoma

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Aim: Hepatic arterial infusion chemotherapy (HAIC) for advanced HCC has sometimes been delivered using percutaneous implanted reservoir-catheter systems (PIRCs). However, several complications are caused by the long-term use of a PIRC. Because of the complications, continuation of treatment may become impossible. At our hospital, we have introduced System I, which is a catheter system that was specifically designed for these cases. In this study, we investigated the efficacy and safety of HAIC using System I. **Methods:** 30 patients who received HAIC using System I were enrolled. **Results:** The HAIC regimens were as follows: CDDP (4), CDDP+5-FU (15), epirubicin+MMC (9), or miriplatin (2). The best-response and disease-control rates were 38% and 82%, respectively. Serious complications were not observed. **Conclusion:** Our results suggest that HAIC with System I is useful for advanced HCC and may provide an option for the treatment of advanced HCC in cases that are difficult to treat with PIRC.

P17-2

IFN- α /5-FU Combination Therapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombus

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Introduction: The prognosis of patients with advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombi remains poor. We have performed combination therapy of interferon (IFN)- α /5-fluorouracil (5-FU) for such advanced HCC. **Method:** The therapy was performed in 60 patients with the advanced HCC. 30 patients received the therapy after palliative hepatic resection. The remaining 30 patients were treated with the therapy as a postoperative adjuvant after curative surgery. **Results:** In the patients with the therapy after the palliative surgery, 10 (33.3%) patients showed objective response. The survival in patients with

objective response was significantly better than that without objective response. In the remaining 30 patients with the IFN- α /5-FU adjuvant treatment, postoperative survivals were significantly better than those in historical controls. **Conclusion:** The combination therapy may be a promising postoperative treatment for the advanced HCC.

P17-3

Radiotherapy for Portal Vein Tumor Thrombosis with Hepatic Arterial Infusion Chemotherapy for Hepatocellular Carcinoma

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Aim: To evaluate the response and survival on 3-dimensional conformal radiotherapy (3D-CRT) for PVTT (Vp3/4) combined with hepatic arterial infusion chemotherapy (HAIC) for advanced hepatocellular carcinoma (HCC). **Methods:** Eighty advanced HCC patients with PVTT (Vp3/4) treated with HAIC were enrolled in this retrospective study. The response and overall survival (OS) were compared between RT group (HAIC combined with 3D-CRT for PVTT) and non-RT group (HAIC alone). **Results:** The objective response of PVTT was significantly higher in RT group than in non-RT group, while that of intrahepatic tumor and MST were not significantly different. Among non-responder to HAIC, MST were significantly longer in RT group than in non-RT group, and the combination of 3D-CRT with HAIC was an independent contributing factor for OS. **Conclusions:** 3D-CRT for PVTT combined with HAIC could play a potential role as a salvage therapy in non-responder to HAIC.

P18-1

New Technique Using Virtual Ultrasound Sonography Software "VINCENT" before RFA

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Objective: SYNAPSE VINCENT is a 3D image analysis system produced by FUJIFILM in Japan. One application of VINCENT is virtual ultrasound software. We evaluate the usefulness in performing the RFA safely and easily compared with volume navigation system like V-NAVI or RVS. **Methods:** 126 HCC nodules were treated by RFA using both volume navigation system and VINCENT. **Results:** VINCENT was found to have clear advantages in the setup time to simulate puncture line and predicted ablation area – especially areas obscured by lung. It is easy to understand the positional relationship to nearby vessel or the intestinal tract. In addition VINCENT is able to be used on over 100 electronic chart PCs throughout the hospital anytime, anywhere compared with volume navigation system. On the other hand, volume navigation system like V-NAVI or RVS has the advantage of using real time imaging. **Conclusion:** Using virtual ultrasound software "VINCENT" is very useful to perform RFA safely and conveniently.

P18-2

Accurate Evaluation of Ablative Margin by Radiofrequency Ablation Using SPIO MRI: Relationship with Local Recurrence

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Background: We have developed a new evaluation method for RFA using SPIO-MRI (SPM), allowing clear 3-D ablative margin (AM) evaluation (Radiology 251:557–65, 2009). **Aim:** We aimed to clarify the relationship between the AM by SPM and the LR of HCC. **Method:** 67 classical HCCs were registered. RFA was done after SPIO injection and AM was judged by MRI 3 to 5 days later. AM were classified into 3 types: AM(+), AM completely encircled the tumor; AM(0), AM partly discontinued; AM(–), AM partly discontinued with tumor protrusion. Re-ablation was performed for AM(–), while AM(+) or AM(0) were closely followed with CT or MRI.

Results: SPM allowed clear 3-D AM evaluation in 96% of HCC. 2 year LR was 3.1% for AM(+), while it was 10.8% for AM(0) tumors ($P = 0.06$). 2 year LR of HCC with AM ≥ 2 mm was significantly lower than HCCs with AM < 2 mm (0% vs 15.8%; $P = 0.04$). **Conclusion:** AM ≥ 2 mm was associated with reduced LR. SPM can also objectively evaluate RFA technique and feedback, a great help for its education.

P18-3

Proton-Beam Radiotherapy: An Effective Alternative Not-Indicating a Curative Treatment for Locally Unresectable HCC

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This phase II trial was conducted to determine the efficacy and toxicity of proton beam radiotherapy for patients with locally unresectable hepatocellular carcinoma (HCC). Eligible patients included single or localized multiple HCC, sized less than 5 cm with in BCLC-A stage. Ten fractionated 66 Gray daily radiotherapy was directed within 2 weeks. Fourteen patients have completed treatment being followed up for a minimum of 3 months, with a median follow-up of 14 months. The mean age was 70 years, and average tumor size was 2.8 cm. Post-treatment toxicity were well tolerated. One and two-year actuarial data showed a 100% local tumor control rate and an overall recurrence rate was 40%, and all recurred tumors were out-field recurrence. Over-all survival rate was 100%, and all of patients responded to treatment. In conclusion, proton-beam radiotherapy is an effective alternative for not indicated for curative treatment of locally unresectable HCC in BCLC guideline.

P19-1

Consensus on Prevention, Diagnosis and Management of Hepatocellular Carcinoma in India: The INASL Recommendations

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HCC is a major cause of mortality in patients with cirrhosis. There are no consensus guidelines on HCC in India. The Indian National Association for Study of the Liver (INASL) set up a Task-Force on HCC, to develop consensus guidelines for diagnosis and management of HCC, relevant to clinical practices in India. The Task-Force identified various contentious issues on various aspects of HCC and used the Oxford

Levels of Evidence for developing an evidence-based approach. Round table discussion was held on 9–10th Feb, 2013 at Puri, Odisha, to discuss, debate, and finalize the consensus statements. The members of the Task-Force formulated the INASL consensus statements for each of the issues. These INASL consensus guidelines (The Puri Recommendations) on prevention, diagnosis and management of HCC in India will be published this year. These are the first guidelines for management of HCC in India and will guide the Indian physicians and surgeons who manage this condition in India.

P19-2

Introduction of Taiwan Liver Cancer Network

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The establishment of tissue bank is very important for cancer research. Hepatocellular carcinoma (HCC) is the most important cancer in Taiwan. Taiwan Liver Cancer Network (TLCN) was organized by coordinated five major medical centers in Taiwan to collect tumor tissues, blood biosamples and clinical data of liver tumor patients. All participating centers must follow a common protocol to collect biosamples and the patients' clinical, pathological and epidemiological information. By Feb. 28, 2014, this network has successfully collected more than 7,000 liver cancer patients with biosamples and clinical information. So far, we already have 87 applications, and have sent out more than 30,500 biosamples. Our Applicants have published 31 papers. The success of Taiwan Liver Cancer Network will become an important resource for the molecular biomarker research for HCC research not just in Taiwan, but also for the world through international collaborations.